

CANNABIS: A PATENT STORY

EXPLORING THE HIGH

Introduction

The most amazing fact about the Mother Nature is that it has provided us with reasons for birth and reason for death of all its creations, and by way of this it maintains balance. Through advancing life, mankind is encountered with various challenging situations and every time Nature provides us with a clue towards life. As we interact more with nature with our knowledge, we are striving more towards life and its challenges. Alzheimer's disease (AD) is one of most challenging neurodegenerative disorders and we are exploring the clue to encounter this through Nature itself.

It is an interesting fact that symptoms of Alzheimer and those of “the High” with Cannabis or Marijuana or Bhang or Ghanja are exactly in contrast with each other. And, perhaps for the same reasons, Nature is providing mankind with a clue to cure the other. Alzheimer causes difficulties with words, speaking or writing, planning or solving problems, familiar tasks become challenging to complete, misplacing things and being unable to retrace the steps, time and place confusion, difficulty understanding visual images and spatial relationship, loss of interest in work or social activities, poor judgement, mood or personalities changes etc. Cannabis, on the other hand, gives a feeling that can be categorized as happy or relaxed, euphoric, giggly, amused, creative, and makes more sensitive to light, color, sound, touch, and smell.

Hence, Cannabis can be considered as one of the excellent natural supplements for an Alzheimer sufferer and proving to be most potent compound to manage the behavioral symptoms.



The Ritual

Cannabis has been used in various cultures of world, especially in Asia for ages. In India, Cannabis, because of its medicinal, recreational and healing properties, is considered as a holy plant or a Prasad of Lord Shiva. Cannabis gives in abundance in a sense that almost all parts of this plant are utilized in various ways for welfare of mankind. Rigveda, Atharvaveda, Sushruta Samhita, and other texts of Ayurveda, Cannabis has been mentioned as a curative wonder drug. In these texts, Vijaya is considered as the conqueror, for conquering various ailments viz. pain, digestive disorders dysentery, sexual disorders etc.

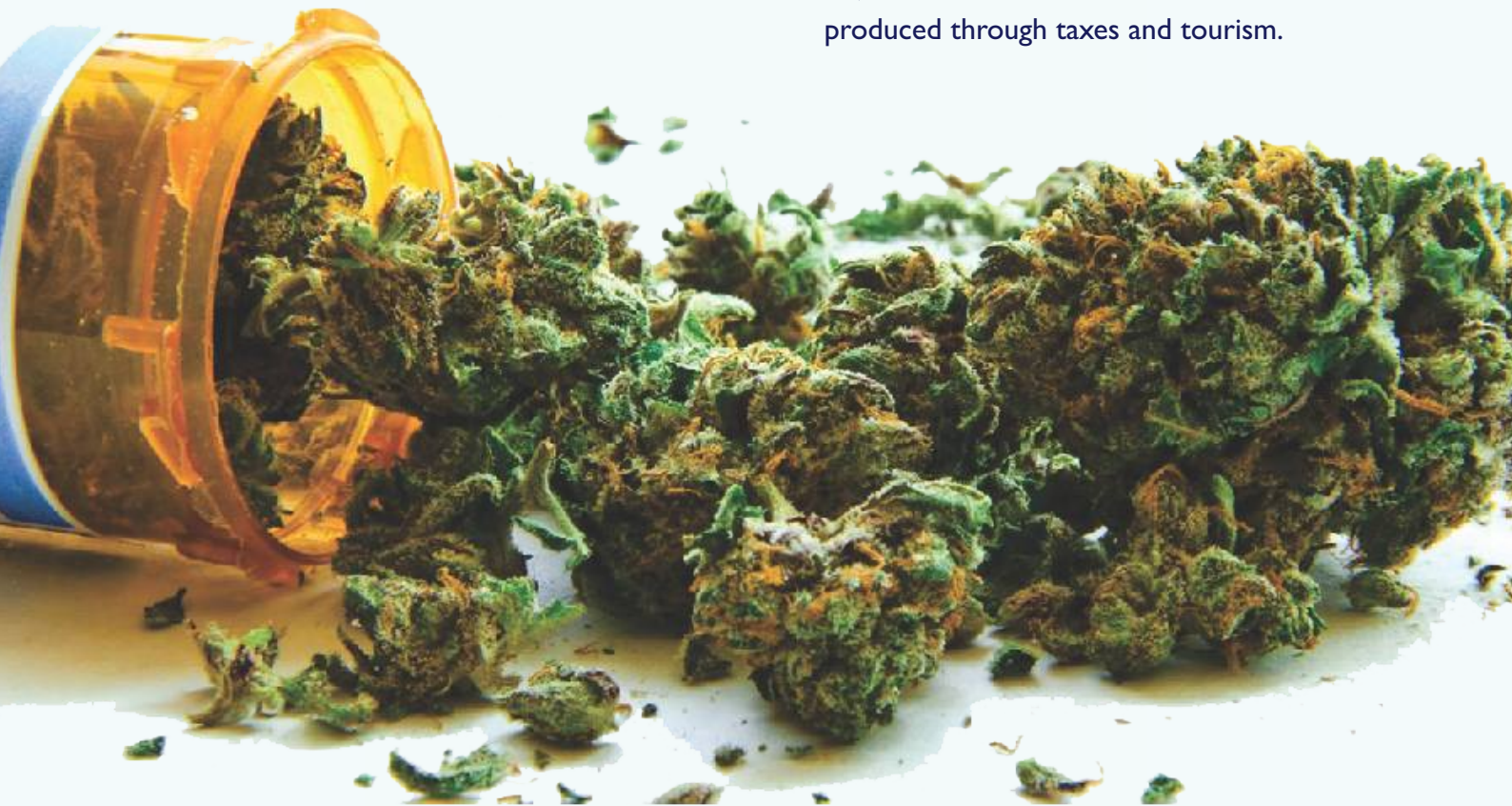
In China, the Taoist encyclopedia, Wushang Biyao mentions Cannabis in a sacred way. In Judaism, although mainstream scholars do not accept the ritual usage of Cannabis, but some scholars like Sula Benet (1967), claimed that the plant named 'Kanrh bosm' has been mentioned five times in the Hebrew bible, is actually Cannabis. In the Sufi tradition, cannabis is considered a vehicle to God and a “method to open the mind for the divine.” While intoxication is considered antithetical to Sharia in the minds of orthodox Muslims, Sufis interpret the Qur'an less literally. In modern times, though Cannabis is being used all over the world and has been popular recreationally, yet it has been vilified all along (for being tough competitor of Alcohol industry).



Plant vs. Drug: the Status

Marijuana (Cannabis), despite of being used for many medical treatments and research all over the world, still falls under Schedule I Drug, i.e. a drug, that has no medicinal values and can only damage one's system. On the contrary, in 33 States of USA, medical use of cannabis is legalized; in 11 States recreational use is legalized, decriminalized in various States, and its Commercial distribution is allowed in most of the States. Also, the USPTO has recently granted its first Hemp Plant Patent (July, 2019) to Charlotte's Web Holdings, Inc., on the very basis that it is legal to grow within the threshold, under the 2018 farm Bill.

Recent legalization of Cannabis for personal use in Canberra (Australia, September 2019) has been reported. Canada too has legalized recreational Marijuana (June, 2018). France is starting Cannabis medical trials soon, Mexico all set to legalize cannabis now. It is reported that Czech government will start paying/subsidizing for patient's medical cannabis from 2020. Another interesting fact is that Uruguay, the world's Marijuana pioneer, which was the first country in the world to legalize recreational cannabis, has sold 3000kgs of recreational Marijuana as of mid-2019. Europe, in the next five years, all set to become the world's largest legal cannabis market, where Germany may be the most potent importer; all such news reports from West (and east too) indicate that – Marijuana legalization brings money, and, once the legal cannabis market is finally set into motion, lacs of jobs are created and millions of Dollars are produced through taxes and tourism.



Exploring the High

The idea behind the present race is various recent research reports that claim the treatment and cure of Alzheimer, Cancer, Chronic pain, AIDS, Muscle spasticity, Epilepsy, Movement Disorders, Multiple Sclerosis, Malnutrition, Nausea and vomiting etc. Clinical trials done of late have given positive results and much needed hope to patients worldwide. Much focus of trials is on Alzheimer and Cancer, and, the results as they claim are much rewarding. Recently, prescriptions including Cannabidiol (CBD) have been approved by the US Food and Drug Administration (FDA) that help in treating Epilepsy, a neurological disorder. For another neurological disorder Alzheimer (AD), the best treatment cannabis Strains are high in Tetrahydrocannabinol (THC) and lower in Cannabidiol (CBD), is yet to be approved.

Since the nature of disease is complex, it is unlikely that any one drug or other intervention will successfully treat it. Current approaches focus on helping people maintain mental function, manage behavioral symptoms, and slow down the symptoms of disease. Present medications include Cholinesterase inhibitors and N-methyl D-aspartate (NMDA) antagonists which have known side effects. Alternative treatments have been beneficial in some cases, including- Coenzyme Q10, Omega-3 fatty acids, Coconut oil, Bright light therapy, Aromatherapy, Acupuncture, Herbal medicines etc.

Of late, Cannabis has been chosen as one of the excellent natural supplement for an Alzheimer sufferer that helps manage some behavioral symptoms such as inflammation, depression, aggression, irritability, lethargy, and other symptoms.



Mechanism of Action

Cannabis sativa is an important herbaceous species containing many valuable natural components. It is found in various habitats varying from sea level to the temperate and alpine foothills of the Himalayas, from where it probably spread over the last 10,000 years. The cannabis plant is reported to have 65 cannabinoids which include Cannabigerol (CBG), Cannabichromene (CBC), Cannabidiol (CBD), Δ^9 -THC, and Cannabinol (CBN) are the most relevant in quantity while delta 9-tetrahydrocannabinol (THC) is the major psychoactive compound. The cannabinoid System (CS) comprises of cannabinoid receptors and their endogenous ligands and is responsible for regulating a number of vital functions, such as sleep, appetite, hunger, pain response, stress relief, coordination, and mood to maintain homeostasis or natural balance. The identification of cannabinoid receptors is followed by the detection of endogenous ligands for these receptors. There are two main cannabinoid receptors comprising of Cannabinoid Receptor 1 (CB1) and Cannabinoid Receptor 2 (CB2). CB1 Receptors are primarily found in the brain and central nervous system and have a role in coordination, metabolism, and pain relief while CB2 receptors are mostly found in the immune system with a protective role. They serve as gatekeepers and may accept or reject cannabinoids and signal when certain compounds are needed.

The mechanism of action of cannabinoids is best investigated for Δ^9 -THC (THC, dronabinol) where majority of THC effects are mediated through agonistic actions at cannabinoid receptors. Also, several modes of action of cannabidiol (CBD) have been proposed such as CBD acts as antagonist at the central CB1 receptor and is able to inhibit several CB1 mediated THC effects. CBD may also increase the plasma THC level by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system. Finally, CBD stimulates the vanilloid receptor type 1 (VR1) with a maximum effect similar in efficacy to that of capsaicin. CBD inhibits the uptake and hydrolysis of the cannabinoid anandamide and increases its concentration.

Cannabinoids interact with a large number of neuromodulators and neurotransmitters which includes glutamate, prostaglandins, nor-epinephrine, dopamine, γ -aminobutyric acid (GABA), acetylcholine, histamine, serotonin, and opioid peptides. A number of pharmacological effects have been explained on the basis of such interactions. For example, tachycardia and hyposalivation with dry mouth are mediated by effects of THC on release and turn-over of acetylcholine. One important physiological role of endocannabinoids is neuroprotection. Ischemia and hypoxia in the CNS induce abnormal glutamate hyperactivity and other processes that cause neuronal damage. These processes also play a role in chronic neurodegenerative diseases such as Parkinson's and Alzheimer's disease and multiple sclerosis. The cannabinoid mechanisms for neuroprotection include modulation of vascular tone, inhibition of calcium influx into cells, inhibition of excessive glutamate production and anti-oxidant properties which reduce damage caused by oxygen radicals.

According to Aso and Ferrer, 2014; Ahmed et al., 2015 endocannabinoid function modulates the primary pathological processes of AD during the silent phase of neurodegeneration: neuroinflammation, protein misfolding, excitotoxicity, mitochondrial dysfunction and oxidative stress. Also, CB₂ levels increase in AD especially in microglia around senile plaques, and its stimulation stimulates A β removal by macrophages.

The treatment with cannabinoids for AD appears both more promising and benign. It was reported by Iuvone et al., 2004 that CBD prevented ROS production, inhibited A β plaque formation, and peroxidation of lipids in PC12 cells exposed to A β , limited neuronal apoptosis from caspase 3 reductions, and counteracted increases in intracellular Ca⁺⁺ from A β . While Esposito et al., 2006 disclosed an in vivo model CBD was anti-inflammatory via reduction in inducible nitric oxide synthase (iNOS) and IL-1 β expression and release and inhibited tau protein hyper-phosphorylation in A β -stimulated PC12 neurons.

According to Hergenrather, 2017 patients were treated with a variety of preparations: THC-predominant (2.5–30 mg/dose), CBD predominant, and THCA, mainly in tinctures and confections. Marked benefit was reported on neuroleptic drug sparing, decreased agitation, increased appetite, aggression, sleep quality, objective mood, nursing care demands, self-mutilation and pain control. According to Russo and Marcu, 2017 based on its pharmacology, cannabis components may provide innumerable benefits on target symptoms in this complex disorder:

Agitation	THC, CBD, linalool
Anxiety	CBD, THC (low dose), linalool
Psychosis	CBD
Insomnia/Restlessness	THC, linalool
Anorexia	THC
Aggression	THC, CBD, linalool
Depression	THC, limonene, CBD
Pain	THC, CBD
Memory	alpha-pinene + THC
Neuroprotection	CBD, THC
Reduced Aβ plaque formation	THC, CBD, THCA

Towards Natural Cure: Patent Status

Scale of Patenting Activity

There were identified 34936 unique patent families relating to neurodegenerative diseases from the database, Questel Orbit, during a search exercise. The applications focused are with an earliest priority date 2011 in order to concentrate on the most new-fangled technologies. The patent families focusing only on the Alzheimer diseases drop down to 1192 with a priority date on or after 2011. The figure obtained after extracting the patent families deal with the cannabis for treating Alzheimer diseases. Prior to 2011, the patent filings related to the neurodegenerative disorders had been wide. However, there is still significant filing activity if we focus on diagnosis of Alzheimer from cannabis.

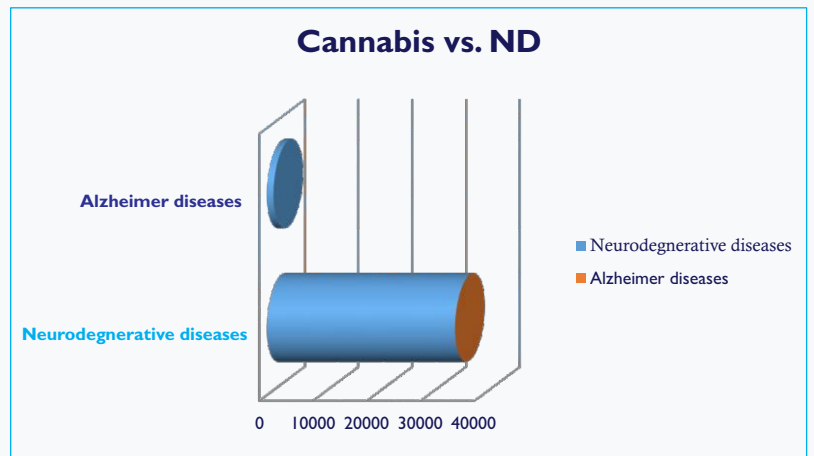


Figure 1: Diseases versus Patent applications

Decade-wise Patents

The decade wise trends of the patent applications have been shown. The trend shows that before 1986, there were no patents related to treatment of Alzheimer diseases but as it has shown a drastic change from 1986 to 2015. The maximum number of patents are filed in the era of 2006 to 2010 which shows the record of 422 followed by the number of patents filed in the year 2001 to 2005 are 293. The least number of patents are filed in the year from 1986 to 1990. After 2015, the number of patents filed is quite large in number i.e. 168.

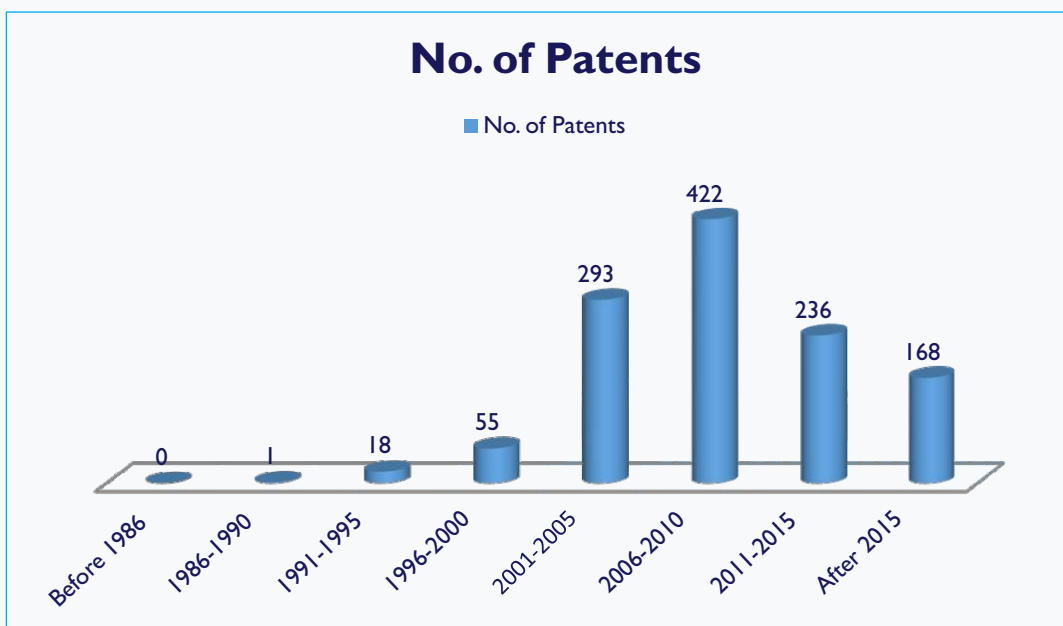


Figure 2: Decade wise patents

Top Players

Figure represents the top players in terms of cumulative patent filing trends. Pfizer appears to dominate from 2011 onwards with over 72 patents filed followed by Esteve Labs, Abbvie, Merck sharp and Dohme, Lund beck and Bristol Myers Squibb. There are several consortiums taking place in this domain. Pfizer with the highest number of patent filings has a turnover of Rs. 1827.74 crores for the year ended March 31, 2015. Pfizer has been developing innovative medicines that effectively treat Alzheimer's disease, autism, bipolar disorder, depression, Parkinson's disease, schizophrenia, among others.

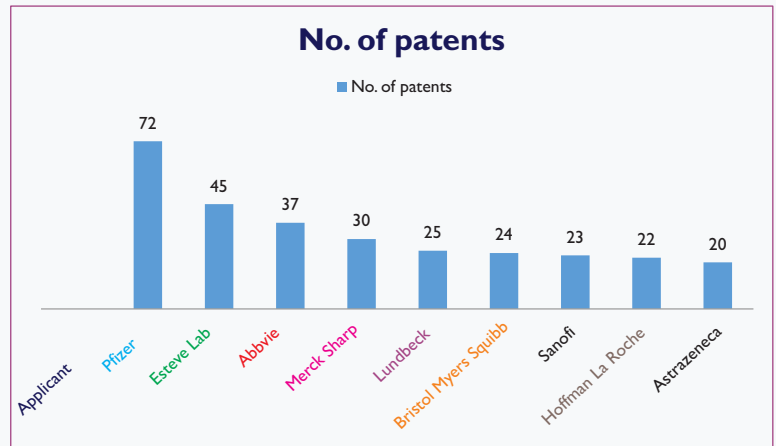


Figure 3: Patent distribution among top companies

Universities

The universities participated in filing patent applications also vary. The University of Connecticut stands first with the highest number of patent filings i.e. 14 followed by university of California which has 6 number of patent filings followed by university of Kentucky which files 3 patent applications. The universities though are not much aware in doing research still coping up with the pharmaceutical companies. The overall universities active in patent filing related to Alzheimer disease are 38.

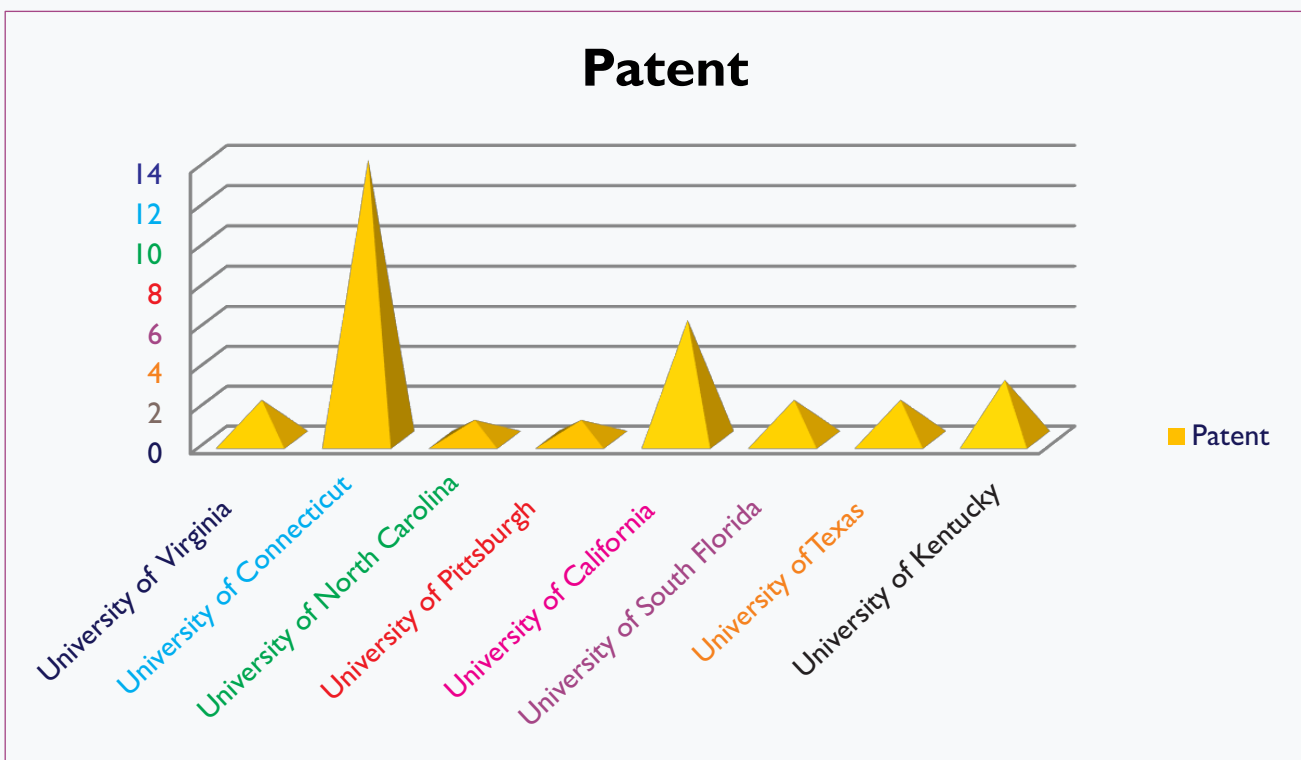


Figure 4: Patent distribution among top universities

Publication Countries

From the publication trend, it appears that the US marks the peak publication mark with around 851 records followed by Europe, Japan, Canada and Australia. The peak trends show the maximum research activity. The US has been building IP for treating Alzheimer disease using cannabis and has been quite consistent and going strong in the years. India ranking in top 10 publication countries has shown 429 patents.

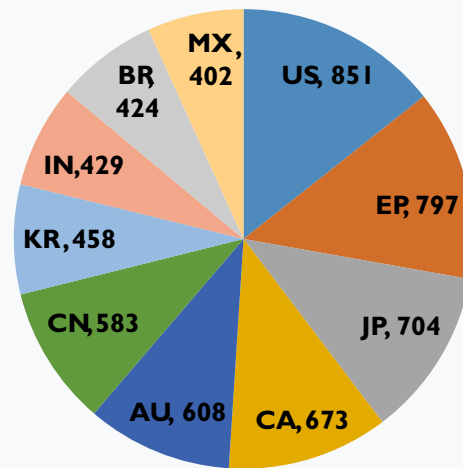


Figure 5: Patent distribution among top publication countries

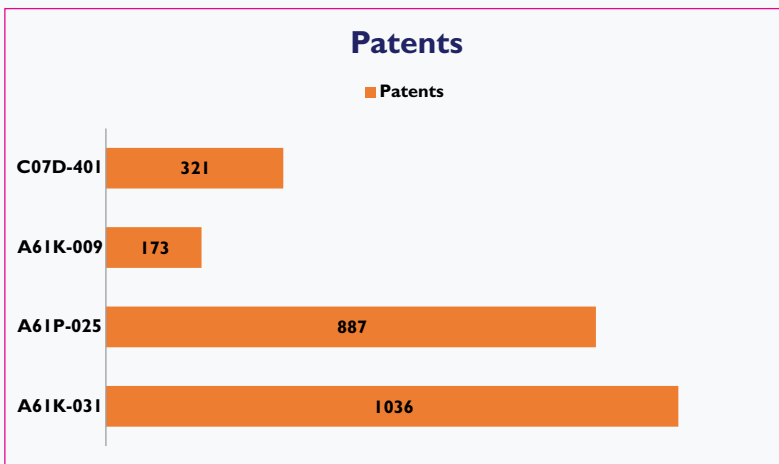


Figure 6: Top IPC classifications

Trends In India

India has been actively participating in building its IP in pharmaceutical industries. India has the most remarkable figures for IP publication for treating Alzheimer diseases with about 429 patent filing which contains 415 alive patents and 14 dead patents. Though there is no sign of patent activities from Indian players but Indian pharma industry is exploiting IP rights includes commercialization of IP-protected pharmaceutical products; exclusive or non-exclusive licensing agreements; the sale or rent or assignment of IP assets; joint ventures etc.

IPC Classifications

IPC classification provides a hierarchical system for the classification of patents and utility models according to the different areas of technology to which they pertain. The graph shows that the top IPC classification deals with the pharmaceutical companies who prepare the compounds containing active organic ingredients followed by the classification that deals with the companies who deals with the drugs for the nervous system disorders trailed by the various compositions for treating nervous system disorders.

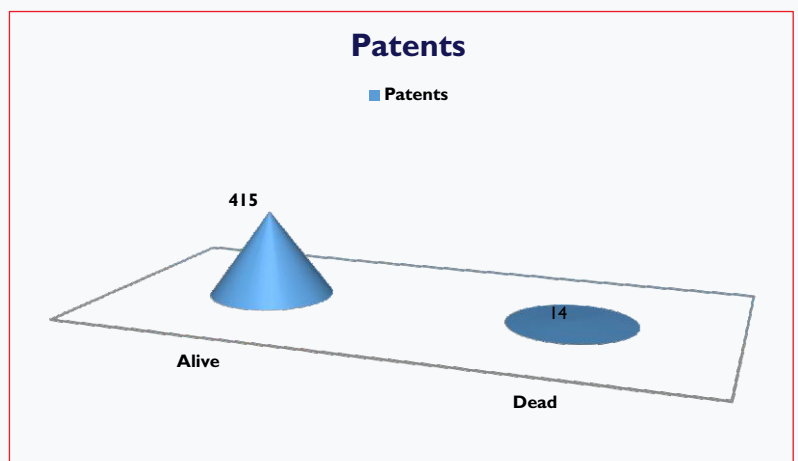


Figure 7: Patent trends in India

Decade-wise

The decade wise trends of the patent applications in India have been shown. The trend shows that before 1995, there were no patents related to treatment of Alzheimer diseases but as it has shown a drastic change from 1995 onwards. The maximum number of patent are filed in the era of 2006 to 2010 which shows the record of 172 followed by the number of patents filed in the year 2001 to 2005 are 119. The least number of patents are filed in the year from 1996 to 2000. After 2015, the number of patents filed is 36.

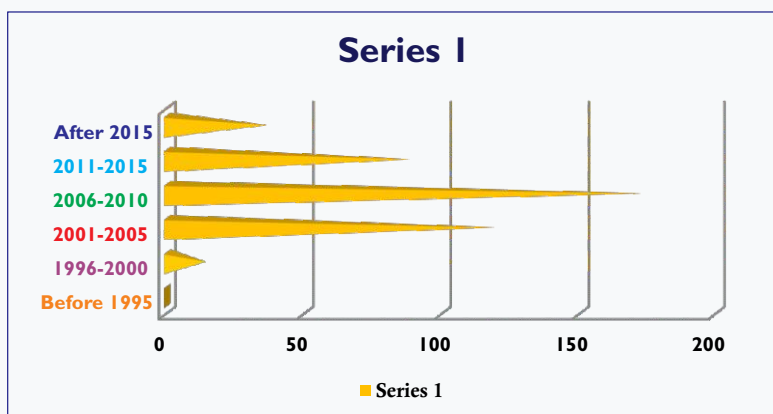


Figure 8: patent Dis tribution decade-wise in India

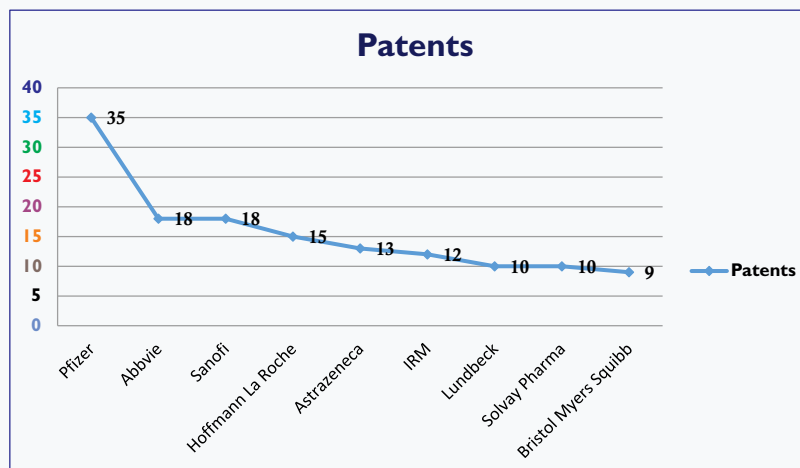


Figure 9: Patent distribution among top companies in India

Top Assignee

Figure represents the top players in terms of cumulative patent filing trends in India. Pfizer appears to dominate with over 35 patents filed followed by Abbvie, Sanofi, Hoffmann La Roche, IRM and Bristol Myers Squibb. There are several consortiums taking place in this domain.

Journals versus Patents

There are overall 1192 relevant patents of various pharmaceutical organizations and universities all across the globe for treating Alzheimer diseases using cannabis and out of 1192 patents, there is no Indian company or Indian University who is working on this domain. As we widen our study from patents to journals, we observe that 1920 research articles and journals have been published worldwide regarding the study of Alzheimer diseases using cannabis and out of 1920 journals, 42 Indian authors have worked on this domain. Though Indian authors have not filed patent but research is still going on and various research articles have been published to show the study of treating Alzheimer diseases using cannabis.

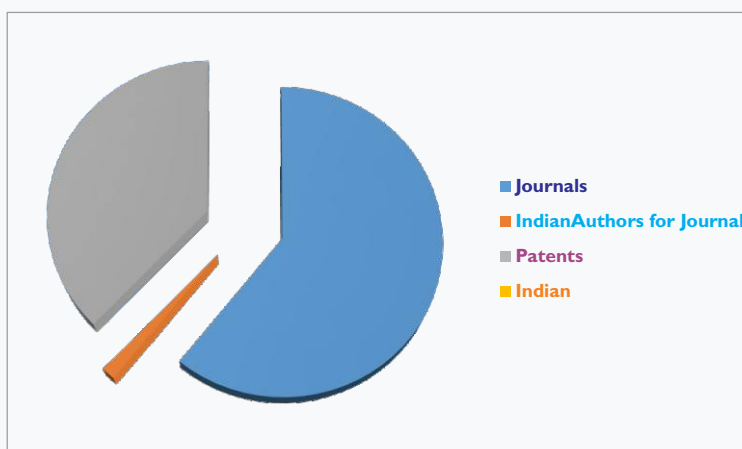


Figure 10: Distribution of Journals and patents among Indian authors

Technology Breakdown

With 1192 patents, approximately 200 patents have been analyzed in depth and have been categorized technology wise. The first category is based on the patent focus. The patent applications mainly focus on the compositions/ compound/ formula for treating Alzheimer using Cannabis and it is recorded as 127.

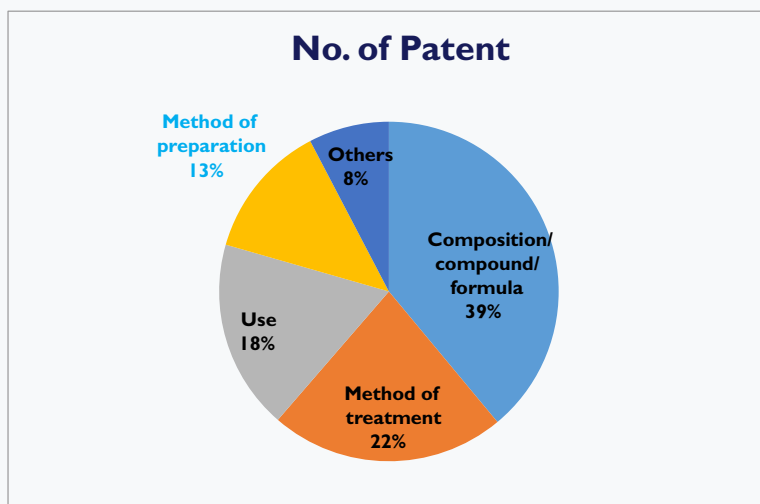


Figure 11: Distribution of Journals and patents among Indian authors

The patent application then deals with the method of treatment which includes 73 followed by the applications which deals with the use and then method of preparation and finally others patent applications which include Kits for use in treating or preventing diseases, a method of modulating, a method of protecting and enhancing the neurological function, method for mitigating a symptom, method for controlling senile dementia, method of ozonizing a non-psychoactive cannabinoid, method of converting a non-psychoactive cannabinoid to a psychoactive cannabinoid, method of suppressing tumor metastasis.

The second category deals with the treatment of Alzheimer diseases using natural and synthetic compounds. The natural compounds used for treating Alzheimer diseases has been only 94 and when it comes in treating Alzheimer diseases using synthetic compounds, it rises to 102. There has been a drastic change in dealing with natural compounds and synthetic compounds of cannabis.

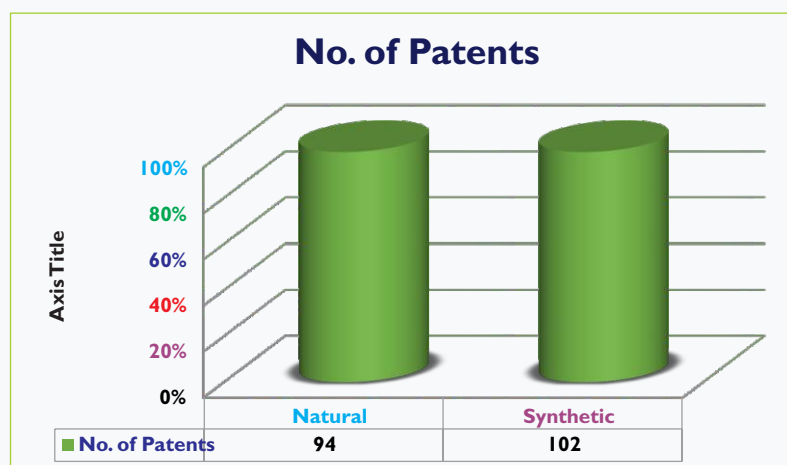


Figure 12: Different components for treating Alzheimer

The third category deals with the mechanism of action for treating Alzheimer diseases. The mechanism of action includes treating Alzheimer diseases using inhibitors that include CB1 receptor, CB2 receptors or both or others. The patent applications that use CB1 and CB2 receptors both are 55 followed by the applications that use CB1 receptor are 38 then trailed by the applications that use other receptors which include glycine and beta-aminobutyric acid and they exhibit anti-proliferative activity.

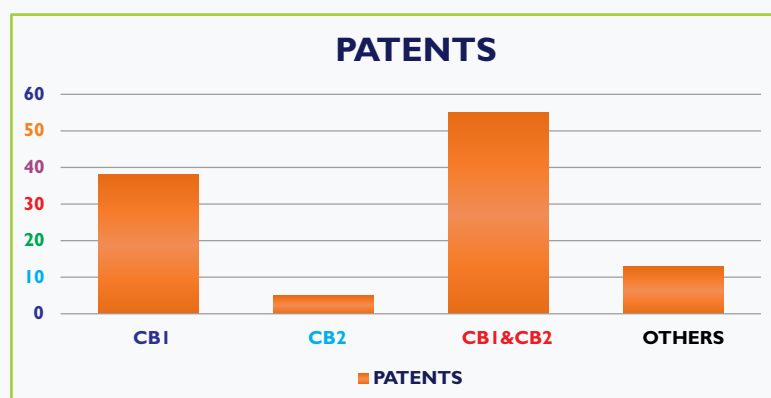


Figure 13: Various receptors used for treating Alzheimer

Emerging Trends

After 2014, the majority of multi-target-directed patents have belonged to private companies. Private companies have thus become the main force attempting to find new breakthroughs among various technologies. **Table I** below shows that most of multitarget-directed patents are in Phase II, while patents granted in 2014–2017 are based on the neurotransmitter theory. This highlights the rapid development of the neurotransmitter theory in the early stages of clinical trials recently.

Table I

Patent No.	Granted year	Drug latest phase	Patentee	Action Mechanism Theory
7939639	2011	Phase III	Pfizer	N, O
8084477	2011	Phase III	Pfizer	N, O
8093276	2012	Phase III	Pfizer	N, O
8642645	2014	Discontinued	Brooks Kelly Research, LLC.	N, O
8802143	2014	Marketed (Launched in 1997)	Center Laboratories, Inc.	N, O
8815288	2014	Marketed (Launched in 1997)	Center Laboratories, Inc.	N, O
8796491	2014	Marketed (Launched in 2004)	Merz & Co.	N, O
8828404	2014	Phase I	Yeda Research and Development Co Ltd	N, A
9011945	2015	Marketed (Launched in 2004)	National Taiwan University	N, O
9034347	2015	Phase II	Louisiana State University	N, O
9066923	2015	Phase II	Blanchette Rockefeller Neurosciences Institute	N, O
9446020	2016	Phase II	Blanchette Rockefeller Neurosciences Institute	N, O
9353084	2016	Phase II; Marketed (Launched in 2001)	H Lundbeck AS	N, O, A
9345685	2016	Phase II	Blanchette Rockefeller Neuroscience Institute	N, O, A
9308175	2016	Discontinued	Echo Pharmaceuticals BV	N, O
9517256	2016	Phase I	Yeda Research and Development Co Ltd	N, A
9664690	2017	Phase II	The National Institute for Biotechnology in the Negev Ltd.	N, O
9616025	2017	Discontinued	Echo Pharmaceuticals BV	N, O
9586904	2017	Phase II	Zhejiang Wanbang Pharmaceutical Plc.	N, O
9675621	2017	Phase II	Wista Laboratories Ltd	N, T
9539235	2017	Phase II	Cognitive Research Enterprises Inc.	N, O

*N represents the neurotransmitter/receptor/signaling dysfunction theory; O represents the other theory; T represents the reduce tau aggregation or phosphorylation theory; A β represents the reducing β -amyloid peptide (A β) production/promoting A β clearance theory.

Generic	Brand	Company	Approved For	Side Effects
donepezil	Aricept®	Eisai	All stages	Nausea, vomiting, loss of appetite, muscle cramps and increased frequency of bowel movements.
galantamine	Razadyne®	Sun Pharmaceuticals	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
memantine	Namenda®	Merz Pharma GmbH & Co. KGaA	Moderate to severe	Headache, constipation, confusion and dizziness.
rivastigmine	Exelon®	Novartis	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
memantine + donepezil	Namzaric®	Actavis and Adamas	Moderate to severe	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, headache, constipation, confusion and dizziness.

Table 2

Table 2 shows U.S. Food and Drug Administration (FDA) approved two types of medications one of them are cholinesterase inhibitors (Aricept®, Exelon®, Razadyne®) and other is memantine (Namenda®) to treat the cognitive symptoms (memory loss, confusion, and problems with thinking and reasoning) of Alzheimer's disease.

Krista Lanctôt of Sunnybrook Health Sciences Center and the University of Toronto tested Nabilone, a synthetic form of cannabis which is currently approved in the U.S. for treating nausea caused by chemotherapy, and used in Canada to treat pain. According to the author, nabilone has shown improved symptoms of agitation and aggression among Alzheimer's disease patients. Sativex® is a peppermint-flavoured mouth spray that contains a 1:1 ratio of two key cannabinoids found in the cannabis plant delta -9- tetrahydrocannabinol (THC) and cannabidiol (CBD). It is a cannabis-based medicine licenced in the UK for the treatment of muscle stiffness and tightness experienced by people with multiple sclerosis. However, Sativex® is not currently licensed in the UK

for any other indication, including treatment of the symptoms of dementia. The *Sativex® for the Treatment of Agitation in Dementia (STAND)* trial will now test whether it's feasible to treat agitation in people with Alzheimer's disease with the drug.

Therefore remarkable progress has been made by scientists in understanding how Alzheimer's disease affects the brain thus promising new treatments to slow or stop the disease.

Conclusion

Nature is an ultimate source of all inspiration, knowledge, and intellect. To harness the best from the nature, we have to identify the real hidden essence which are already created by the nature for the wellbeing of mankind and civilization. As we locate and identify these essence, we are harnessing and opening the secret of knowledge mine layer by layer already existing for the betterment of mankind and ultimately for the betterment of Nature itself.

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