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The hemp plant cannabis sativa, versatile plant named by Swedish botanist Linaeus in 1735 originated in Central Asia has been widely distributed around the world. The earliest use of the drug has been known to be in existence since 700 BC in Assyrian tablets drug finding its place even in the British Pharmaceutical Codex, as late as 1949(G. Geoffrey, W. Brain and R. Philip; 2004).

Cannabis is an annual dioecious developing from seed, fast growing plant which reaches the maturity in 60 days. It has a lance shaped leaflets with saw tooth edge with woody angular hairy stem with a height of 50 ft or more. Cannabis indica is smaller subspecies it a height of 4 feet other varieties are obtained by crossing cannabis sativa and cannabis indica.

Cannabis is used as psychoactive drug. Around 20 million people in USA and Europe and many other part of world use cannabis on a regular basis although consumption is illegal in most of the countries. The psychoactive ingredient of cannabis is delta-9-tetra hydrocannabinol (THC). Cannabis is also known by the names like marijuana, hashish, charas, bhang, ganga and sinsemilla among this hashish and charas are most potent with THC content 10 – 20%. High concentration of THC can be found in the fine droplets of sticky resin produced by glands at the base of the fine hairs that coats leaves and flower heads (J. Robert," A primer of Drug Action; 1998).

Fig 1 Cannabis sativa (http://ja. treknature. com)

Fig 2 Cannabis tincture (http://www. medicalmarijuanacure. com)

History and Development of Cannabis

Fig 3 (M. D. Vincenzo; 2006)

Chemistry of THC:

Chemical structure of THC was elucidated in 1964; thereafter many chemical analogues have been synthesized and tested.

Phenolic hydroxyl group(C-1) is for cannabiniol activity, side chain(C-9) is important as potency can be increased by increase in chain length, also methyl group substitution at side chain carbon adjacent to aromatic ring and northern aliphatic hydroxyl group enhances the activity of THC. THC was isolated during the world war II from red oil fraction of cannabis and other optically active component isolated was cannabidiol. (G. Geoffrey, W. Brain and R. Philip; 2004)

Fig 4 Structures of delta-9-tetra hydrocannabinol(THC)

IUPAC Name: – (âË†')-(6aR, 10aR)-6, 6, 9-trimethyl-3-pentyl-6a, 7, 8, 10a-tetrahydro-6H-

benzo[c]chromen-1-ol

Molecular weight: – 314. 45 daltons.

Formula: – C21H30O2

Pharmacology (Cannabiniod receptor):

First cannabinoid receptor was identified in 1990 which lead to further studies. In central nervous system cannabinoid receptor are found in G-proteins with seven transmembrane spanning segments which are strongly expressed in basal ganglia, cerebellum and hippocampus, at higher concentration expressed on afferent spinal cord regions and at lower concentrations at brain stem it has a chain of 473 amino acids with a hydrophobic domain (B. David, P. Gareth, G. Gavin, and T. Alan; 2003). Second receptor (CB2) is expressed by leucocytes and in haemopoeitic development. Endocannabiniods have cannabinoid receptor binding activity and function of the endocannabinoid system is to regulate synaptic neurotransmission. First endocannabiniod was observed in 1992 by Devan and co-workers from porcine brain which was anandamide it showed behavioural, hypothermic, and analgesic effects similar to that of cannabinoids many other are found in central nervous system (CNS) but exact physiological roles are not yet know (L. A. Matsuda, S. J. Brownstein, et al; 1990).

Fig 5 CB expression on brain.

(B. David, P. Gareth, G. Gavin, and T. Alan; 2003)

Pharmacodynamics:

Effects of THC on CNS studies shows impairment in learning, psychomotor performance and associative processes. Heavy users showed impairment in attention and â€Å“ amotivationalâ€ syndrome with chronic use of marijuana(R. I. Block, R. Fairnpour, and K. Braverman; 1998). Commonly seen physiological effects on cardiovascular system are increased blood pressure, heart rate with dry mouth, dizziness and slight nausea(H. G. Pope and D. Yurgelun-Todd; 1996). Long-term use leads to immunosuppression of immune system, also Cannabiniod receptors inhibit intracellular adenylate cyclase second-messenger system resulting into decrease spleen cell liberation on immune response and increase the susceptibility of infections or disease. Chronic use results into reduction in fertility and sexual potency in the individual.(P. A. Fried; 1995). THC readily passes through placenta and affects the new born with visual perception, language comprehension and frequent memory loss. (M. A. Huestis, A. H. Sampson, B. J. Holicky, et al; 1992)

Pharmacokinetics:

Most commonly cannabis is taken by smoking which is through inhalation followed by rapid absorption from lungs into the bloodstream though bioavailability is less (10-27%). Oral administration has plasma levels much lower compared to Intra-venous infusions and inhalation this is due to first pass metabolism in the liver resulting in to poor bioavailability. Bioavailability

is higher by sublingual and rectal administration. Cannabinoids are lipophilic in nature (log Kow= 7. 4) and gets widely distributed in brain, kidney, liver and fat with steady release in the blood, 90% of cannabinoids are bound to plasma proteins and 10% to red blood cells(M. Wahlqvist, M. I. Nilsson, F. Sandberg, S; 1970). Phase I metabolism of cannabinoids is catalysed by cytochrome P450 in liver with oxidase system. Majority of THC metabolites are excreted in faeces (65%) and rest in urine through glucuronide conjugates (M. Bornheim and A. Correia; 1989).

Tolerance and dependence:

The long known use of the drug has not really given a clear scientifically proven picture that the drug or the derivatives of the plant are beneficial for therapeutic purposes (A. Duffy and R. Milin; 1996). Although there are no severe dependency problems, on the hind side, the toxic nature of Cannabinoids, has also seen increased heart rate, lowering of blood pressure, euphoric intoxication and toxic psychosis resulting from a loss of cognitive performance. Extensive clinical trials over the years have seen the drug being classified into lesser harmful categories, classified into Schedules from 1 to 3, with 3 being of least harm (C. P. O'Brein; 1995).

Funded by Medical Research Council, the research includes testing on 660 patients over a time period of 3 years. Another research involves 400 patients who would be treated with different forms of cannabis plant and compared with conventional analgestics. The trails are supported by nations like UK, USA, Switzerland, Germany with each country supplying the distinct Cannabis extracts. Another trial in UK is for treatment of multiple sclerosis and other neurological disorders and use a sub-lingual spray as the method

of drug delivery. Each of the manufactured extract needs to comply with the Good Manufacturing Practice(s) that oversees selection of plant material, solvent used, and the entire processing itself. (C. P. O'Brein; 1995).

Analytical Methods:

Initial screening of drug of abuse is generally carried out by immunoassay and confirmation of the results is done using chromatographic methods. Radioimmunoassay is generally used for detection cannabinoids in the biological samples. Gas chromatography (GC) is most frequently used analytical method to analyse product but due to decarboxylation during the analysis in neutral forms determination of acidic cannabinoids is not possible. High speed liquid chromatography (HPLC) method used for determination of composition of cannabinoids is one of the efficient and the simplest way to elucidate major cannabinoids but overlapping of peaks is a concern (Y. Ruiqin, X. Wenlin; 2006). Though combination of mass spectroscopy and HPLC rectifies errors due to overlapping of peaks and combination of HPLC/GC can produce effective analysis. (B. Benjamin, D. Benjamin, L. Pierre, T. Laetitia, D. Nathalie, D. Lies, V. Alain, H. Philippe, C. Corinne," Innovative; 2009).

Fig 6 GC chromatogram of a standard solution of D9-THCA-A analysed

(F. E. Dussy et al; 1996)

Fig 7 HPLC chromatogram of THC recorded at 220nm

(F. E. Dussy et al; 1996)

Small amount of sample can be reused with simple operation using solid-phase micro-extraction (SPME) to study cannabinoids followed by GC/MS for target molecule confirmation and determination presence of THC in saliva and hair using SPME-GC/MS can be determined (F. E. Dussy et al; 1996). LC-IT/MS is used for quantification and conformation of various cannabinoids in a single method though this method is cost effective so use is limited.(A. A. M. Stolker, J. van Schoonhoven, A. J. de Vries, I. Bobeldijk-Pastorova, W. H. J. Vaes, R. van den Berg; 2004)

Legalization:

The legal position held on this drug is still in a state of confusion with no conclusive evidence on the actual therapeutic effects it has. Many countries have softened their stand on the punishment for possession of cannabis, with Netherlands going to the extent of decriminalizing soft drugs in 1976. Belgium followed suit, with the clause that it should not lead to social nuisance, risks and problematic consumption. The USA took a U turn to prohibit the drug due to not enough evidence after certain states allowed the use of the drug for medicinal purposes. Canadian law allows the usage of drug for exceptional cases of patients with prior support from the medical practitioner.

Due to its activity on the nervous system, the drug has primarily been used in medicinal treatment of muscle spasms, menstrual cramps, rheumatism, tetanus convulsions, rabies and epilepsy with the current day applications being witnessed in treatment of anorexia, bronchial asthma, epilepsy, glaucoma, hypertension, muscle spasticity, nausea, vomiting and pain. But these applications have just fetched two licensed cannabinoids for medicinal

purpose – THC (Marinol) and Nabilone, both of which are synthetic (A. C. Moffat; 2006).

Conclusion:

The Cannabis plant (Cannabis sativa.) is used as recreational drug with a long history

and is a part of traditional medicine from the past. The relatively recent discovery of cannabinoid receptors and the human endocannabinoid system has opened up a new and exciting field of research. Bioavailability is obtained by rectal and sublingual administration and rapid absorption takes place with intra-venous and inhalation. But despite the potential, cannabis is categorized as a narcotic drug it is prevented to develop into modern medicine. Dependence and addiction to this drug is quite rare. Psychoactive cannabinoid tetrahydrocannabinol (THC) has received great attention, and much is known about its biological effects and mechanisms of action, analytical methods, pharmacokinetics, and structure-activity relationships, it will be a challenge to see cannabis as a routine medicine for various disorders.