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RESEARCH ARTICLE

FUTURE OF CANNABIS IN DENTAL PRACTICE

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Abstract

Implications of Cannabis in medicine are gaining popularity with every new day whereas its implications in the field of dentistry is a topic least discussed about. Introducing Cannabis into dental practice can reshape the future of the latter towards the brighter side upon aware and calculated use of the former. Both the dental professional and the patient can benefit from the pharmacology of Cannabis.

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Introduction:-

Cannabis refers to the drug which comes from the flowers of the female Indian hemp plants such as Cannabis sativa and Cannabis indica¹. Cannabis can be derived from the plant in 3 main forms as-

1. Marijuana:

It is the dried leaves of the Cannabis flower and also the least potent form of Cannabis.

2. Hashish or Hash:

Hashish is the dried resin of the Cannabis plant and is comparatively more potent than the Marijuana.

3. Hash oil:

It is the natural resin of the Cannabis flower and is golden brown in colour. It is the most potent form of Cannabis.

The Cannabis plant has a distinct appearance with bright green leaves and are arranged in a pattern of 5-7 leaflets. The flowers of the cannabis plant are covered with a thick resinous material. Cannabis sativa has been used for medicinal purposes throughout the human history². The first records date back to ancient China around 5000 years ago². This flower and the resin of the female Cannabis plant contains hundreds of chemical compounds which are known as cannabinoids. The two most important cannabinoids identified from the Cannabis plant are Delta-9-Tetrahydrocannabinol(THC) and Cannabidiol(CBD). THC is a psychoactive agent whereas CBD has no psychoactive abilities.

Endocannabinoid system:-

The Endocannabinoid system is a highly specific and localised system widely distributed in the Central Nervous System³. The Endocannabinoid system, as of what we know today comprises of two Endocannabinoid receptors namely Endocannabinoid receptor-1 and Endocannabinoid receptor-2 and the corresponding ligands N-Arachidonylethanolamine(also known as Anandamide) and 2-Arachidonoylglycerol(also known as 2-AG)⁴. The Endocannabinoid system is distributed over the spinal and supraspinal region which makes it a prime position for regulation of neurophysiological activities and alterations in this system could provide a mechanism by which depression, pain, stress and anxiety coexist⁶.

Additionally, there is strong scientific support for its use in eating disorders, to reduce vomiting and nausea associated with chemotherapy, and to alleviate Human Immunodeficiency Virus infection and Acquired Immune Deficiency Syndrome (HIV/AIDS) related weight loss^{7,8}.

Cannabis and the Endocannabinoid system:-

According to the World Drug Report 2017, Marijuana is consumed by up to 238 million people worldwide, making it, by far, the most widely used drug⁸. The cannabinoids found in the Cannabis interact with the Endocannabinoid system in the human body. The psychoactive cannabinoid Delta-9-tetrahydrocannabinol, upon consumption causes psychoactive effects which include euphoria, appetite stimulation, sedation, altered perception, impairments in motor control and memory deficits⁸. Even though Delta-9-tetrahydrocannabinol has psychoactive effects, it has therapeutic value and unique applications⁸.

On the contrary, Cannabidiol is a non-psychoactive compound⁸. Consequent of its non psychoactive character, it is of utmost medical importance⁸. Studies have proven Cannabidiol of anti-inflammatory, antioxidant, anti-epileptic, antirheumatic, anxiolytic and analgesic properties^{8,9}. Apart from these, Cannabidiol was also shown to reduce congestion and nausea and to be neuroprotective^{8,9}. Infact, Cannabidiol positively modifies the effects of Delta-9-tetrahydrocannabinol by reducing its psychoactive abilities and increasing its clinical efficacy and duration of its clinical benefits^{8,10}.

An enduring notion in the field of medicinal Cannabis is that of the entourage¹¹. In 1998, Professors Raphael Mechoulam and Shimon Ben-Shabat posited that the Endocannabinoid system demonstrated an “entourage effect” in which a variety of “inactive” metabolites and closely related molecules markedly increased the activity of the primary endogenous cannabinoids, Anandamide and 2-Arachidonoylglycerol¹². This helped them to explain how the botanical drugs were often more efficacious than their isolated counterparts¹².

Implications in dentistry:-

Dental anxiety:-

Dental treatment still remains as one of the most anxious visits despite awareness between dentists and patients in building trusting relationships. The fear of dental treatment determines the frequency of treatment availed with long-term implications in oral health maintenance¹³. This high level of fear of dental treatment can have an appreciable impact on the community¹⁴. First, people with dental fear or anxiety tend to delay or avoid dental visiting and secondly, these patients with high levels of dental anxiety may prove difficult to treat, require more time, and present with behavioral problems which can ultimately result in a stressful and unpleasant experience for both the patient and the dental professionals¹⁴.

Consequently, these patients, because of their fear or anxiety of dental treatment and having avoiding a dental treatment can have poor oral hygiene. These patients can undergo through various non-pharmacological techniques of anxiety and/or fear management. However if none of the non pharmacological techniques bring about appropriate results, a pharmacological approach can always be made. Currently available pharmacological treatments include Serotonin reuptake inhibitors, Serotonin–Norepinephrine reuptake inhibitors, benzodiazepines, monoamine partial 5-hydroxytryptamine (5-HT)_{1A} receptor agonists but however these medications are associated with limited response rates and residual symptoms and adverse effects may also limit tolerability and adherence¹⁵.

Cannabidiol can be a new drug of choice for anxiety management. Preclinical and clinical studies show that Cannabidiol has wide range of therapeutic effects such as antipsychotic, analgesic, neuroprotective, anticonvulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties¹⁵. A review of potential side effects in humans found that CBD was well tolerated across a wide dose range, up to 1500 mg/day (orally), with no reported psychomotor slowing, negative mood effects, or vital sign abnormalities noted¹⁵. The Endocannabinoid system, especially the Endocannabinoid receptor-1 are integral to the regulation of fear and anxiety management. Anxiolytic action of the Cannabidiol can be attributed to its interaction with the Endocannabinoid receptor-1 and other receptors responsible for regulation of anxiety or fear such as the Serotonin 5-HT_{1A} receptor, and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptor¹⁵. Hence, administration of Cannabidiol could alleviate anxiety and lead to a successful dental treatment.

Pain:-

Pain is a complex psychological perception and there are several points in pain pathways that the cannabinoids may exert actions on. Mechanical, thermal, and chemical signal transduction occurs via TRP channels, acid-sensing channels, and adenosine receptors on peripheral nociceptors¹⁶. Cannabinoid receptors are found in all of the nociceptive neuroanatomical pathways mentioned. Infact, they participate in descending supraspinal pain modulation via the Periaqueductal Gray and Rostral Ventromedial Media¹⁶. The principal actions of Endocannabinoid receptor-1 decrease pre-synaptic intracellular calcium concentrations and activate inward-rectifying potassium channels which depress neuronal excitability and reduce transmitter release¹⁶.

Attributing to its analgesic properties, Cannabis can make an appreciable impact on the ongoing opioid crisis. In 2016, the opioid crisis was responsible for 42,000 overdose fatalities in the United States¹⁷. Moreover, more than 25 million adults in the United States suffer from chronic pain¹⁷. Apart from the concern of overdose, another major concern with long term opioid use is opioid addiction. Opioid addiction is a chronic mental illness that causes the addicted individuals to experience many relapses and remissions throughout their life, and they suffer from many uncomfortable symptoms, including tolerance development and withdrawal¹⁸. Also, opioids cause undesirable side effects that include nausea, vomiting, abdominal pain and constipation that are collectively referred to as “opioid induced bowel dysfunction”¹⁹.

Cannabidiol, a non-psychoactive, analgesic cannabinoid could be used against opioids due to its lack of side effects over long term use. Individuals who use cannabis to manage chronic pain may be at a lower risk for cannabis use problems, a study indicates²⁰.

Apart from the patients undergoing dental treatment, pharmacological benefits of Cannabis can be reaped by dental professionals alike. Musculoskeletal pain is a major health burden among dental health professionals. Musculoskeletal pain occurs as a result from pain of muscles, joints, ligaments, bones, tendons, blood vessels and other supporting structures such as intervertebral discs²¹. Some studies have reported that musculoskeletal diseases and pain considerably contribute to reduced productivity and poorer quality of work, decreased job satisfaction, occupational accidents, sick leave, and leaving the profession via premature retirement²¹. Cannabis can also be used by dental professionals to treat musculoskeletal pain as a pharmacological approach along with other non-pharmacological management such as physiotherapy.

New cannabis strains- A patient personalised approach:-

2011 was a landmark year for Cannabis genomics, as Medical Genomics and Nimbus Informatics issued an online report on the complete 400 million base-pair genomic sequence, which was shortly joined by a draft genome and transcriptome¹⁰. By 2011, the enzymes for the production of the major cannabinoids had been identified. Similarly, selective advanced Mendelian breeding yielded Cannabis varieties rich in specific single components. Thus, high-THC and high-CBD plants were produced for pharmaceutical development, along with analogous breeding of other minor cannabinoids¹⁰. These different strains with different ratios of Delta-9-tetrahydrocannabinol to Cannabidiol could prove beneficial to the dental professional in providing a personalised medication for the patient. A patient personalised approach could aid in laying a strong foundation of a dentist-patient relationship.

Versatility in routes of administration:-

Even though the routes of administration of Cannabis are diversified, the pharmacokinetics of cannabinoids and the effects observed depend on the formulation and route of administration, which should be tailored to individual patient requirements. The pharmacokinetics and the effects observed with Cannabis medicines depend on the formulation and route of administration²². Cannabinoids administered via inhalation exhibit similar pharmacokinetics to those administered intravenously. Inhaled Cannabidiol has an average systemic bioavailability of 31%, and a plasma concentration–time profile similar to that of Delta-9-tetrahydrocannabinol²².

Even though, smoking Cannabis is the most common route of administration, it still accounts for increased respiratory disorders and poorer oral health which is undesirable when seeking a dental treatment. Use of vaporiser to administer Cannabis can avoid respiratory risks and also the exposure to toxic pyrolytic compounds formed via combustion²². Moreover, Inhalational or oromucosal delivery of cannabinoids avoids or reduces the extensive first- pass metabolism observed following oral cannabinoid administration²².

Oromucosal preparations undergo rapid absorption via the oral mucosa (and hence are useful for symptoms requiring rapid relief), producing plasma drug concentrations higher relative to oral, but reduced relative to inhaled THC. However, part of the dose may be swallowed and orally absorbed²².

Transdermal administration of cannabinoids avoids first-pass metabolism but their extremely hydrophobic nature limits diffusion across the aqueous layer of the skin. Effective skin transport can only be obtained by permeation enhancement²².

Antimicrobial action:-

Antimicrobials that kill or inhibit infectious diseases are essential clinical tools, yet resistance continues to emerge, diversify, and spread rapidly. Globally, antimicrobial-resistant infections kill at least 700,000 people each year. Within 30 years, resistant infections are predicted to kill 10,000,000 per year, greatly exceeding deaths from cancer²³. This apocalypse of resistance is estimated to become the greatest challenge in healthcare by 2050²³.

The risk of a bacterial infection causes threat to dental patients who need to undergo invasive dental treatments. Antibiotic resistance and emergence of new antibiotic resistant bacteria pose a greater threat due to lack of availability of therapeutic options. To battle antibiotic resistance, there is an urgent need for development of new antimicrobial agents and alternative strategies that are effective against antibiotic resistant strains of bacteria. The need for the new antimicrobial agents and the parallel legalisation of Cannabis fueled the research for its many therapeutic aspects in many countries around the world²⁴.

Results from a research conducted for therapeutic aspects of Cannabis showed that Cannabidiol displayed a substantial inhibitory effect on Gram-positive bacteria with minimal inhibitory concentrations ranging from 1 to 2 µg/mL²⁴. Time kill analysis and minimal bactericidal concentration revealed potential bactericidal activity of Cannabidiolic acid and Cannabidiol²⁴. While cannabinoids showed a significant antimicrobial effect on the Gram-positive *Staphylococcus aureus* and *Staphylococcus epidermidis*, no activity was noticed on Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa*. Cannabidiolic acid presented a two-fold lower antimicrobial activity than its decarboxylated form²⁴. In fact, both Cannabidiolic acid and its decarboxylated form (Cannabidiol) presented low hemolytic activity on the human red blood cells and the safety of Cannabidiol toward human keratinocyte cells presents no toxicity at a concentration of up to seven-fold higher than the antibacterial minimal inhibitory concentration²⁴. Similarly, both Cannabidiol and Cannabidiolic acid are well tolerated by mammals, including humans, and conserve a safe value limits for blood-contacting drug development²⁴. Overall, Cannabidiol exhibited a strong antimicrobial effect against Gram-positive strains and could serve as an alternative drug for tackling Gram-positive bacteria and some antibiotic resistant strains such as the Methicillin Resistant *Staphylococcus Aureus* (MRSA)²⁴.

Addiction or dependence:-

As discussed above, about the ongoing opioid crisis and the significant threat of overdose and addictive nature of the opioids, Cannabis is emerging out as a breakthrough replacement of opioids with potent analgesic properties and comparatively less addictive behaviour against opioids. Research suggests that increasing adult access to both medical and recreational Cannabis has significant positive impacts on public health and safety as a result of substitution effect²⁵. Concluding results of study showed that the growing body of research supporting the medical use of Cannabis as an adjunct or substitute for opioids creates an evidence-based rationale for governments, health care providers, and academic researchers to consider the implementation and assessment of Cannabis-based interventions in the opioid crisis²⁵.

Role of a dental professional:-

Since, Cannabis has been finally accepted of its therapeutic activities, it's the role of the dental professional to be aware of the pharmacodynamics and dosage of the Cannabis. A dental professional should be knowledgeable of the legalisation laws and the regulation and routes of administration of Cannabis. However certain precautions must be taken during administration due to other drug interactions that may occur. Cannabinoids bind to many members of membrane transporters e.g. ATP-binding cassette superfamily including breast cancer-resistant protein (BCRP) and Glycoprotein P (P-gp)²⁶. Interactions of cannabinoids with BCRP and P-gp have been reported in preclinical studies²⁶.

Conclusion:-

Cannabis has proved its therapeutic potential when addressing the issues faced during a dental procedure such as dental anxiety, post-operative pain etc. With the legalisation of Cannabis, it is surprising to note that it isn't introduced yet in the dental practice, but doing so shall provide a promising future for both Cannabis and dentistry. Aware and calculated use of Cannabis in dentistry could bring about a harmonious balance for both the profession and the drug.

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