

Cannabinoids in Inflammatory Modulation of Allergic Respiratory Disorders and its Pharmacotherapeutic Approaches to central Respiratory disorders

**Aruna Gundluru¹, Debanjan Mitra², Dr. K.S.Bhosale³,
Dr. Ashish Kumar Jha⁴, Ganesh Suresh Tolsarwad⁵**

**¹ Associate professor, Department of obstetrics and gynecological
Nursing, Sree narayana nursing college
milkyanu87@gmail.com**

**² Research scholar, Department of Microbiology
Raiganj university, WB, India
debanjanmitra267@gmail.com**

**³ Department of Botany, Nowrosjee Wadia College Pune
ksbhosale@gmail.com**

**⁴ Head, Department of Zoology, Hislop College, Nagpur
ashishjhahislop@gmail.com**

**⁵ Assistant Professor, Pharmacy
Swami Vivekanand College of Pharmacy, Udgir
tolsarwadganesh988@gmail.com**

Abstract

The study has clearly provided an idea of anti-inflammatory responses of Cannabinoids against respiratory disorders. In that case, asthma can be considered as one of the major diseases and most of the individuals have been suffering from it. In that case, “human endocannabinoid system” can be considered as one of the complicated structures that are mainly responsible for producing signals. Therefore, the entire system of ECS includes ligand, enzymes, synthesis process and degradation. Cannabinoids can be obtained from the plant Cannabis Sativa plant. On the other hand, cannabinoids have the anti-inflammatory properties which can exacerbate the activation of CB2 signalling pathways. The study also demonstrates the derivative substances of cannabinoids has involved the inflammation process and also focuses on the immune responses. In this study, there were mainly two types of receptors mentioned and both of them belong from the G protein family. CB2 cells mainly activate and release proinflammatory mediators, which mainly act on the respiratory inflammation and also help in reducing the impact. In contrast, the activation of CB1 receptors directly impacts the bronchial nerve endings and it can be taken as a positive aspect for treating asthma.

Keywords: Immune response, cannabis, inflammation, cannabinoids, CB1, ECS, CB2

Introduction

Allergic respiratory disease mainly occurs due to the rapid exposure of allergens which can leads to the formation of inflammation at the respiratory tract. Furthermore, this disease can

show the symptoms of dyspnoea and cough. Due to rapid industrialization, most of the individuals have been suffering from asthma. The respiratory tract of human beings is mainly responsible for exchanging gases like O₂ and CO₂, however presence of some foreign materials such as bacteria, virus, pollen and smokes can form a barrier during gaseous exchange. Sometimes Asthma can be chronic and incurable in nature, hence it can be considered as one of the major economic burdens for healthcare systems from all over the world. The study is going to shed light on the role of Cannabinoids in treating the inflammatory disease of the respiratory tract.

A naturally found substance is cannabinoid, that can be easily detected from the plant *Cannabis sativa*. From this plant materials there are near about 480 complicated compounds present, within which only 66 plant materials are termed as cannabinoids. In that case, marijuana or Cannabinoids have been utilising for therapeutic approaches since centuries. The compounds found in the plant cannabis can help in the chemical purification process. Human nervous systems have a specific type of cannabinoid receptors, which can act as a cloned part and also foster the ligand binding process. In this way, cannabinoids can be further used as a novel therapeutic approach for treating inflammation in the respiratory tract of human beings.

Literature review

Different types of allergic respiratory disorders

Asthma can be considered as one of the major inflammatory diseases of human being which can be further known as atopy. Predilection is one of the major characteristics of asthma and the reaction can be observed against the foreign materials within the cells. Therefore, multiple risk factors have been associated with the formation of asthma. A rapid wheal and Flare reaction can be observed after the participation of antigen and after that Ige become captured and also cause the formation of hypersensitivity. As a result, it may gradually form the inflammation of the reaction site and due to the great affinity towards the Ige receptor, it will further activate different types of cells such as eosinophils and dendritic cells [1]. Before the manifestation of clinical aspect of asthma or inflammation Ige also help to activate the histamines.

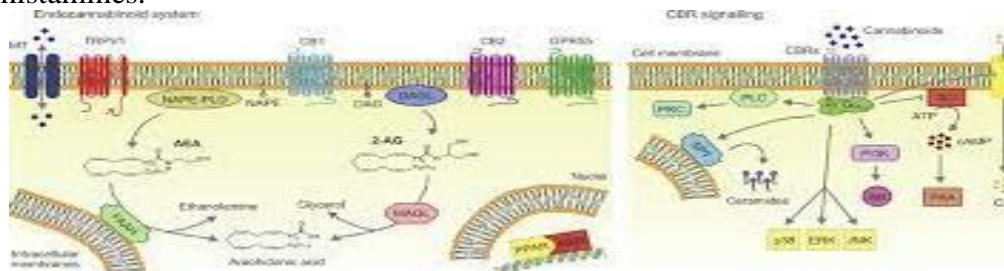


Figure 1: Process of inflammatory reaction

Source: [1]

On the other hand, respiratory disease or inflammation can be occur due to some other types of pathogens. All these pathogens always target the obstruction in airways and in order to cope with this situation, cells may release acetylcholine which can foster the phenomena of mucus secretion from the area of the reaction. The proper characteristics of inflammation and lung disorder incorporates the production of antigen mediated IgE and IgG cells [2]. Due to the reaction of antibodies within the cell, a hypersensitive mechanism is formulated. This phenomena of hyper sensitive mechanism is responsible for robust inflammation in the cells, in this way asthma can generate some other types of allergic reactions such as allergic rhinitis. In that case, it can be observed that rhinitis generally occurs at the upper respiratory tract and due to the inflammation, the lower part of the respiratory tract is also affected. In that case, the lower part may receive hyper secretion of mucus and airway hyperresponsiveness.

Impact of cannabinoids on inflammation and allergic disorders

Immune system of human beings is generally made up of innate and adaptive immunity. In

that case, after entering the pathogens inside the body, the innate immunity can deliver a quick response however, the adaptive immunity provides a slow response. Innate immunity can react against the pathogens and gradually eliminate those substances from the body of individuals and helps in returning towards the homeostasis phase [3]. Since decades, cannabis and its products has been utilised in treating the inflammation, however a lack of proper knowledge hampering the utilisation of cannabis for further treatment process. Some other studies have proven that inflammatory responses are observed in the in vivo and clinical studies. It can be further used as a mediator in keratinocytes, as a result high usage of cannabis is able to decrease the effect of inflammation.

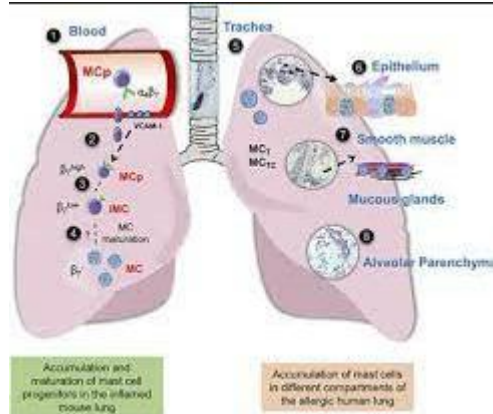


Figure 2: Impact on respiratory tract

Source: [3]

On the other hand, it can be observed that, human nervous system including the Endocannabinoid system can modulate a variety of physiological activities such as blood circulation, reproductive system and also endocrine system. In that case, ECS can be denoted as one of the major factors that can cause a wide range of inflammation and is also beneficial for clinical perspective [4]. The system of ECS can incorporate both receptors of inflammation in respiratory tract such as CB1 and CB2 receptors. Additionally, during inflammation in the respiratory tract some other receptors such as peroxisome proliferators and TRPA also get activated. ECS also have the receptors for the binding activities of ligands and also responsible for secretes enzymes for endocannabinoid metabolism. Further expression of immune cells is intact during the presence of endocannabinoids in that case, CB2 plays an important role and express more in comparison to CB1 receptor. Therefore, the regulatory activities of CB receptors are mainly responsible for the anti-inflammatory responses.

Pharmacotherapeutic approaches of cannabinoids to central respiratory system

In the case of pharmaceutical approaches, the biomolecules of cannabis play an essential role for reducing the impact of inflammation. Cannabis can generate a wide range of Phyto Cannabinoids which can be denoted as oxygenated hydrocarbons [5]. Apart from that some other alkyl substitutes and meroterpenoids can be derived from the hydrocarbons. Within the plant materials the acid becomes decarboxylated and the presence of an odd number of carbon atoms can be recognised within the structure.

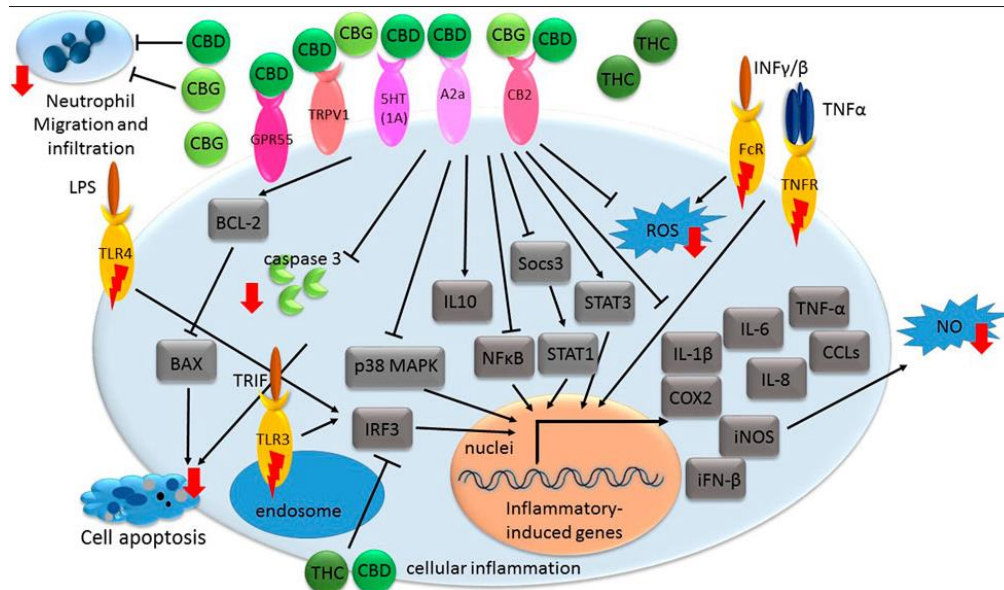


Figure 3: Working mechanism of cannabinoids

Source: [6]

According to some previously conducted experiments it can be stated that cannabinoids have the capability to act against inflammation. This anti-inflammatory mechanism follows a specific pathway which includes some Toll-like receptors. These receptors can activate the MAPK signalling pathway and NF-κB activation, which should induce the proinflammatory genes. The stimulation of macrophage, monocyte and macroglia, after the signalling pathway, is able to generate LPS stimulation [6]. During inflammation, the molecules of cannabinoids support the signalling process of TLR. In that case the activation of TLR can enhance the CBR expression and also the production of endocannabinoids. With the help of metabolic pathways, cannabinoids can provide indications to mediate the effect of inflammation. Activities of the immune system are always governed by the macrophages, T cells and DCs. After entering of antigens, Immune responses should be activated, and it is linked with glycolysis anabolic process. Henceforth, the body of human beings is required to form a tolerance state against the inflammation. The tolerance stage is related to the catabolic process, and AMP kinase is the major regulator of this process. Autophagy, oxidative phosphorylation and biogenesis are some common catabolic methods that occur against inflammation [13]. There are near about 30% of the population are generally affected due to the allergy and it may directly impact on type 2 helper T cells. This allergic disease can be further divided in two distinct parts such as effector phase and Sensitization phase.

Materials or methods or methodology

The methodology part of the study can be taken as an essential portion, which can prove a deep insight on the particular topic. Therefore, the collection of information should be conducted after acquiring a proper process. In that case, a secondary qualitative data collection method has been chosen for this purpose. Secondary data can be easily gathered by anyone from the internet, just after a single click. In this process, anyone can collect data by searching it on authentic websites. Secondary data or information are cost effective and anyone can obtain a bulk of information from websites. Additionally, some other sources of secondary data are websites, journals, books and articles. This particular topic can be found on the websites of PubMed and also google scholar. PubMed is one of the authentic websites which contains genuine medicine related journals, articles and books [7]. The site PubMed also has more than 35 million citations and it is one of the reliable sites for taking information for this research. On the other hand, PubMed also provides medical subject training to the individuals, hence it can be considered as an online library for medical journals.

The particular topic for the study is mainly to cover the proper utilisation of cannabinoids in

treating respiratory disease. However, in some countries the usage of cannabinoids is not legal and sometimes medicine manufacturing industries do not have sufficient knowledge regarding the usage of cannabis. In that case, the particular study can provide the pharmaceutical usage of cannabinoids and its positive impact on reducing respiratory inflammation. In this way, individuals can get the data of other researchers from the scholarly journals. On the other hand, some countries in the UK have already permitted the usage of cannabis for medical purposes. The collection of secondary data can help in the process of comparison between different countries and also help in evaluating the benefits of using cannabinoids. Inclusion criteria for this study are, journals should be collected only from the authentic government websites [8]. All relevant journals should not be older than the year 2018, henceforth the study should be more valid for the other individuals. For this study, there are some exclusion criteria and there should be more than 20 relevant articles chosen for accomplishing the study. Journals or information from irrelevant sources should not be included for this purpose. With the help of secondary data, the study can be more diverse and reliable for others.

Discussion

The above-mentioned literature can help individuals to understand that chronic and acute inflammatory disorders can lead to the disruption of an organ's activities. In that case, since decades cannabis has been used for treating inflammation and allergic disorders of respiratory tracts. Inflammation can be occurred due to the rapid reaction of monocytes after entering the pathogens in the body [9]. In that case, monocytes are generally discharged from the bone marrow and travel through the blood into the specific tissue of respiratory tract or inflammation sites. It can be observed that after the maturation of macrophages the damage or injury become more significant. The utilisation of cannabinoids may trigger the release of anti-inflammatory properties and also activates three other mediators such as phagocytes, immunomodulation and antigen presentation. The study also provided an illustration of a specific signalling pathway which is highly related to the suppression of the reaction by the Phyto cannabinoid mediated system. Therefore, cannabinoids contain some specific binding properties which can directly connect with the receptors and lead to conveying and interacting with the anti-inflammatory responses. In that case, the treatment of cannabinoids includes some components such as "THC- Δ^9 -tetrahydrocannabinol", "GPR- G protein-coupled receptor", "CB- cannabinoid receptor", "MAPK" and "COX" [10]. On the other hand, the presence of TNF- α , generally responsible for releasing chemokines, interferon alpha, beta and gamma factors. When inflammation occurs, it gradually passes a signalling response through some pathways such as MAPK, "nuclear factor kappa B" and TLR pathways. As a result, the activation of such pathways can cause the activation of target genes after enabling the phosphorylation process.

The study also provided the concept of using cannabinoids as a precaution against respiratory inflammation. Henceforth, after using cannabinoids as a drug, it can be observed that, the properties of cannabinoids can activate two types of receptors such as CB1 and CB2 [11]. In addition, it can be denoted that, CB1 has the high impact on the cells of the brain whereas CB2 is mainly responsible for the inducing immune response. Human body can produce endocannabinoids and also transmits endogenous ligands for CB1 and CB2 receptors. As a result, CB1 can successfully suppress the previously occurred inflammation. There are near about 100 Phyto cannabinoids and its positive influences can be detected till now. In this context, only tetrahydrocannabinol has the capacity to bind with both CB2 and CB1. The Human immune system can deliberately express the endocannabinoid's molecules, which plays an essential role in generating the immune response. Therefore, the role of CB2 receptors is significant for this study and the presence of THC in the lymphocytes is able to produce immune responses [12]. The Presence of T lymphocytes can be highly expressed by the CB1 activities. Further activities can induce the activation of B lymphocytes that can trigger the formation of IgE and IgM. Mediation of endocannabinoids occur depending on

CB2 and CB1, hence cannabinoids can be taken as an essential influential factor for generating the adaptive and innate immune responses against respiratory inflammation.

Conclusion

The study has demonstrated knowledge regarding the molecular mechanism of ECS and its relation with cannabinoids. In recent years, Cannabinoids can easily regulate a different type of physiological methods and the further improvement can be observed in past years. Depending on this advancement, the medical sector has decided to use cannabinoids in the clinical aspects or the therapeutic approaches. Previous studies have illustrated that cannabinoids are responsible for the exacerbation of Asthma and it can further activate the CB2 dependent signalling pathway. The molecules of cannabinoids are small and easily targets the components of ECS. Asthma can be allergic and it is obstructive in nature, that directly impacts on lungs of human beings. In the case of pathogenicity of Asthma is experimental and the activation of T helper cells act as a mediator. Cannabinoids can be obtained from the plant cannabis Sativa and it encompasses amino acids, metabolites and terpenoids. In recent years, it can be observed that cannabinoids have antioxidative and anti-inflammatory properties. The usage of cannabinoids can enhance the production of glucocorticosteroid hormones. Cannabinoids have the following anti-inflammatory properties such as “ Δ -9-tetrahydrocannabinol (THC)”, “ajulemic acid (AJA; C₂₅H₃₆O₄)” and “2-arachidonoyl glycerol (2-AG)”.

References

1. Corrado, A., Battle, M., Wise, S.K., Lee, F.E.H., Guidot, D.M., DelGaudio, J.M., Molina, S.A. and Levy, J.M., 2018, October. Endocannabinoid receptor CB2R is significantly expressed in aspirin- exacerbated respiratory disease: a pilot study. In *International forum of allergy & rhinology* (Vol. 8, No. 10, pp. 1184-1189).
2. Dietrich, A., 2019. Modulators of transient receptor potential (TRP) channels as therapeutic options in lung disease. *Pharmaceuticals*, 12(1), p.23.
3. Ghasemiesfe, M., Ravi, D., Vali, M., Korenstein, D., Arjomandi, M., Frank, J., Austin, P.C. and Keyhani, S., 2018. Marijuana use, respiratory symptoms, and pulmonary function: a systematic review and meta-analysis. *Annals of internal medicine*, 169(2), pp.106-115.
4. Ghasemiesfe, M., Ravi, D., Vali, M., Korenstein, D., Arjomandi, M., Frank, J., Austin, P.C. and Keyhani, S., 2018. Marijuana use, respiratory symptoms, and pulmonary function: a systematic review and meta-analysis. *Annals of internal medicine*, 169(2), pp.106-115.
5. Graczyk, M., Lewandowska, A.A. and Dzierżanowski, T., 2021. The therapeutic potential of cannabis in counteracting oxidative stress and inflammation. *Molecules*, 26(15), p.4551.
6. Jacobo, A.A.M.P.D. and Palomares, L.A.O., 2020. The Role of Cannabinoids in Allergic Diseases.
7. Khodadadi, H., Salles, É.L., Shin, E., Jarrahi, A., Costigliola, V., Kumar, P., Yu, J.C., Morgan, J.C., Hess, D.C., Vaibhav, K. and Dhandapani, K.M., 2021. A potential role for cannabichromene in modulating TRP channels during acute respiratory distress syndrome. *Journal of Cannabis Research*, 3(1), pp.1-7.
8. Kicman, A., Pędzińska-Betiuk, A. and Kozłowska, H., 2021. The potential of cannabinoids and inhibitors of endocannabinoid degradation in respiratory diseases. *European Journal of Pharmacology*, 911, p.174560.
9. Levy, J.M., 2020. Endogenous cannabinoids may regulate chronic inflammation in aspirin-exacerbated respiratory disease. *World Journal of Otorhinolaryngology-Head and Neck Surgery*, 6(04), pp.255-257.
10. Milad, N. and Morissette, M.C., 2021. Revisiting the role of pulmonary surfactant in

- chronic inflammatory lung diseases and environmental exposure. *European Respiratory Review*, 30(162).
11. Mugnaini, C., Rabbito, A., Brizzi, A., Palombi, N., Petrosino, S., Verde, R., Di Marzo, V., Ligresti, A. and Corelli, F., 2019. Synthesis of novel 2-(1-adamantanylcaboxamido) thiophene derivatives. Selective cannabinoid type 2 (CB2) receptor agonists as potential agents for the treatment of skin inflammatory disease. *European Journal of Medicinal Chemistry*, 161, pp.239-251.
 12. Scheau, C., Caruntu, C., Badarau, I.A., Scheau, A.E., Docea, A.O., Calina, D. and Caruntu, A., 2021. Cannabinoids and inflammations of the gut-lung-skin barrier. *Journal of Personalized Medicine*, 11(6), p.494.
 13. Timalisina, D., Pokhrel, K.P. and Bhusal, D., 2021. Pharmacologic activities of plant-derived natural products on respiratory diseases and inflammations. *BioMed Research International*, 2021.
 14. Warren, C.M. and Zaslavsky, J.M., 2022. Should cannabis be a higher priority for allergists?: A history and look down the pipe. *Annals of Allergy, Asthma & Immunology*, 129(4), pp.393-394.