Review Article

International Research Journal of Ayurveda & Yoga
Vol. 4 (12),115-124, November, 2021
ISSN: 2581-785X; https://irjay.com/
DOI: https://doi.org/10.47223/IRJAY.2021.41218

Immune Modulating Theorem of *Vijaya Ghrita*, A Fast Acting Ayurvedic Cannabis Formulation for Treating Covid-19 Disease Symptoms

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Article Info

Article history:
Received on: 12-10-2021
Accepted on: 02-12-2021
Available online: 31-12-2021

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ABSTRACT:

Covid-19 is an infectious disease caused by airborne virus SARS-CoV-2 was declared as global pandemic by WHO on 11th March 2020. Medical community is facing challenges in developing anti-viral medicines and vaccines, as various mutations in novel coronal virus are causing hurdles in formulating an effective remedy. Environment is crowded with many microorganisms including pathogens like virus, bacteria, fungi, parasites etc. Hence immunomodulation (redirecting immunity to natural course) is the best way to tackle such pandemic situations. Ayurveda, the Indian system of medicine is the oldest science known to mankind has quite a few medicines and therapies to improve immune system. *Vijaya* (*Cannabis sativa* Linn.) is the one of the *Divyaushadhi* (celestial plant) mentioned in Ayurveda having *Rasayana* (Rejuvenative), *Vyavayi* (fast diffusing) and *Yogavahi* (synergetic) attributes. On the basis of Ayurvedic principles we made an attempt to interpret the immune modulating aspect of a rare Cannabis formulation *Vijaya Ghrita*, presumed to be liposomal medication that has swift bio-enhancing ability. Ayurvedic properties of the ingredients of *Vijaya Ghrita* found in classical texts could treat most of the symptoms of Covid-19 disease and the contemporary scientific researches of Cannabis phytochemicals on Covid-19 have shown significant results in reducing the pro-inflammatory cytokine storm, also to certain range halt the entry, replication of SARS-CoV-2.

Key Words: *Vijaya*, Cannabis, COVID-19, SARS-CoV-2, Main protease, Cytokine storm.

INTRODUCTION

Novel corona virus transmission is mostly by droplet infection and is also airborne through aerosols like droplet nuclei causing Covid-19 pandemic. Breathing is the primary means of survival and practically one cannot wear 24/7 an N-95 FFR masks and still there is a 5% probability of infection as they filter close to 95% of 0.3µm size particles. Concerning point is less than 2.5µm aerosol particles associated with SARS-CoV-2 were also detected.[1] There is no effective remedy till date, as the SARS-CoV-2 virion undergoes genetic mutations during its continuous replication which may lead to the alteration of virus surface proteins and antigens. These variants show signs of resistance to existing treatment options leading to repeated change in treatment protocol.[2]

Immune system is our first line of defence against

pathogens and also revitalise body by initiating tissue repair. Immune boosters are recommended by the ministry of AYUSH in the protocol of Covid-19 for better recovery and to maintain good quality of life.[3-4] In Ayurvedic literature, *Pancha karma* (purification therapies) to detoxify the channels of body, *Rasayana aushadha* (rejuvenative medicines) to improve the immunity and symptomatic treatment are the general line of treatment in addressing Covid-19 like pandemics named as *Janapadodhwamsa* or *Maraka*. [5]

MATERIALS AND METHODS

Potent immunomodulating medicines are required to improve immune system responses to tackle quickly spreading infectious pandemics like Covid-19. We chose *Vijaya* (*Cannabis sativa* Linn.) to be the core of formulation because it is a *Rasayana* (rejuvenating & adapto-immuno-neuro-endocrino-modulator properties), *Medhya*[6] (nootropic or brain tonic that help maintain the neuronal health and psychological balance) *and Vajikarana oshadhi*[7] (aphrodisiac herb) said to be originated from ambrosia as per *Vedic* mythology.[8] *Vyavayi*[9] (catalytic or fast diffusing), *Yogavahi*[10] (synergetic) properties of *Vijaya* (*Cannabis sativa* Linn.) gives the advantage of quick action, greater bioavailability and potentiation of other ingredients used along. *Tikshna guna*[11] (sharp attribute) is another quality of *Vijaya* which quickly enhances the metabolism, expels morbid *Dosha* (waste substances) helping in purification of body said by commentator Hemadri. We selected the Cannabis based Ayurvedic medicine available in the market *Vijaya Ghrita*, taken from a classical book *Bharat Bhaishajya Ratnakara* listed in the first schedule of drugs and cosmetics act (1940).[12] We also explored online journals for scientific research articles on PubMed, Elsevier, Google Scholar, ResearchGate, ScienceDirect, Medline, Semantic Scholar, Ayush research portal, etc, related to Cannabis therapeutics for Covid-19 disease and immune modulation.

RESULTS

Vijaya Ghrita is a *Vajikarana* (aphrodisiac) formulation prepared by traditional method of *Ghrita paka* (cooking in medicated Ghee) infusing *Vijaya* (*Cannabis sativa* Linn.) and Cow-Milk in Cow-Ghee that proclaim *Sukra stambhana* property (retention or control over loss of *Sukra Dhatu*).[12] There are *sapta dhatu* (seven primary tissue elements) in a human body where *Sukra* is the seventh *dhatu*.[13] Aphrodisiac medicines maintain healthy *Sukra dhatu* that can be compared to the tissues and components of reproductive system present in both males and females.[14-17] In general the digested food nourishes each *dhatu* one by one from *Rasa dhatu* (blood plasma) to *Sukra dhatu* in a time span of one month. [18] Advantage of aphrodisiac herbs is they nourish *Sukra dhatu* directly bypassing the exhaustive time taking process.[19]

Ojas (immunity) is the *Vyadhiksamatwa* (defence against diseases) whose prime actions are divided into curative named *Vyadhibala-virodhatvam* (capacity of the body to fight against the diseases) and preventive called *Vyadhiutpada-pratibandhkatvam* (capacity of the body to prevent the manifestation of pathogenesis).[20-21] *Ojas* (immunity) is the most important element for maintaining and sustenance of life.[22] There is a relation between aphrodisiacs and *Ojas* (immunity). *Sukra dhatu* pervades in every cell of the body (*Sarvatra* a*nugata*),[14] same as *Ojas* that is circulated in whole body.[23] *Acharya Charaka* postulated *Suka* and *Ojas* as one of the vital elements of life (*Pranayatana*)[24] and *Acharya Susruta* also mentioned *Ojas* as the best abode of life (*Pranayatana uttamam*).[25] *Sukra* is the par excellence of well digested food[26] which is later converted to *Ojas*, the immune components. Hence *Ojas* (immunity) is promulgated as the *Upadhatu* (tissue derivatives) of *Sukra dhatu*.[27] Diminished *Sukra* may lead to many diseases and even death, so one should preserve *Sukra dhatu* by indulging in wholesome food and lifestyle.[26] Hence potent *Vajikarana* (aphrodisiac) herbs especially *Sukra Stambhana oshadhi* (drugs promoting retention or control over loss of *Sukra Dhatu*) like *Vijaya* (*Cannabis sativa* Linn.),[28] can pause the depletion of *Ojas* (immunity) along with improving its quantity.

Tri-dosha (fundamental bio-elements viz- *Vata*, *Pitta* & *Kapha*) are responsible of every physiological function.[29-30] In the above formulation, main ingredient *Vijaya* (*Cannabis sativa*) is *Vata-Kapha* alleviating ambrosial herb;[31] Cow-Ghee is predominantly *Vata-Pitta* alleviating with *visha-hara* (eliminating toxins), *Balya* (invigorating),[32] *Sukra-vardhaka* (enhances *Sukra Dhatu*), *Ojo-vardhaka* (immune enhancing) property; [33] Cow-Milk is *Vata-Pitta* pacifying with *Rasayana* (rejuvenating), *Jivaniya* (vitalizing/ supporting life)[34] attributes similar to *Ojas* (immunity)[35] which positions *Vijaya Ghrita* formulation as an excellent *Tri-dosha* balancing medicine that quickly improves immune system. Table-1. Shows Research articles on Cannabis related to immune modulation, lung tissues and Covid-19.

DISCUSSION

Briefly stating all immune cells arise from precursors in the bone marrow (a unit of *Majja Dhatu*) which develop into mature cells through a sequence of alterations that can occur in different parts of the body. Hyper-immunity or auto-immune response is a result of aberrant immune components.[53] As per Ayurveda *Majja Dhatu* (6th primary tissue element) is responsible for the formation of *Sukra Dhatu* (7th primary tissue element)[54] whose essence (*Upadhatu*) is *Ojas* (immunity).[27] In the classical texts the treatment for deranged *Majja Dhatu* and *Sukra Dhatu* are similar.[55] Ayurvedic basic principles are gold standard which can be explicated by another simple example. As per Ayurveda *Ojas* (immunity) circulates all over the body along with *Rasa dhatu* (blood plasma).[56] This deciphering of an age old vedic principle explain why plasma donation[57] was once an off label therapy for Covid-19 patients as Ojas/ antibodies (immune components) are in circulation with blood plasma, but was removed from Covid-19 treatment protocol as the antibodies in donor's plasma were not adequate enough for patient recovery and also researchers speculated the risk of new variants of virions by mutations between different strains of SARS-CoV-2. [58]

Common Covid-19 symptoms are fever, dry cough, tiredness with shortness of breath and severe inflammation as serious symptoms. Other symptoms are runny nose or nasal congestion, headache, loss of taste or smell, aches, myalgia, sore throat, chest pain, loss of appetite, nausea, diarrhoea, etc.[59-60] Hypercytokinemia, commonly known as Cytokine storm is an acute raise in circulatory levels of pro-inflammatory cytokines triggered by the uncontrolled hyper-activity of deranged immune system caused by SARS-CoV-2 in the respiratory tissues that results in decreased oxygen intake by damaging the endothelium of air-sacs (alveoli) and capillaries (small blood vessels).[61] Micro-vascular thrombosis (micro blood clots) or embolism resulting from the damaged walls within the pulmonary circulation triggered by hyper-coagulation, immune-thrombosis (caused by deranged immunity) is the reason for hypoxemia (decreased oxygen saturation in blood) in Covid-19 patients. [62-64]

The herbal ingredient in the above formulation, *Vijaya* (*Cannabis sativa* Linn.) has a unique relation to the human body. The main compounds in Cannabis plant called phytocannabinoids viz- CBD (cannabidiol), THC (tetrahydrocannabinol), CBG (cannabigerol), CBC (Cannabichromene), etc, are similar (analogues) to endocannabinoids produced naturally inside the body viz- Anandamide (N-arachidonoylethanolamine), 2AG (2-Arachidonoylglycerol), etc, which function under ECS (endocannabinoid system). The ECS is an important neuroendocrine-modulatory system in the mammals. It comprises of endogenous cannabinoids, cannabinoid receptors viz- CB1, CB2, etc and the enzymes responsible for the synthesis and degradation of endocannabinoids to maintain homeostasis.[65] These receptors are present all over the body particularly CB2 receptors that mostly express in immune system are postulated to be involved in every physiological function.[66] Other important phytocompounds in Cannabis plant are terpenes and flavonoids which in combination produce the therapeutic effect.[67-68]

Ayurvedic and modern research both reveal Cannabis potentiality in treating majority of Covid-19 symptoms. *Vijaya* (*Cannabis sativa* Linn.) properties as per Ayurveda are *Jwaraghna* (anti-pyretic),[69] *Sankramaka Kasa hara* (cures infectious cough),[70] *Tamaka Swasa hara* (cures bronchial asthma),[71] *Ruchya* (improves taste),[72] *Dipana* (appetiser), *Pachana* (digestive), *Grahi* (Absorbent),[11] *Ajirna hara* (cures indigestion), *Atisaraghna* (anti-diarrhoeal),[73] *Manasika dourbalya hara* (heals psychological weakness),[74] *vak vardhini* (helps to clear speech disorders and sore throat)[11]. As *Vijaya* (*Cannabis sativa* Linn.) is a *Vata-Kapha* alleviating herb[31], it is used for treating pain & inflammatory disorders like *Nadi dourbalya* (neuropathies),[75] *Ardhavabhedaka* (migraine),[76] *Siro-vyadha* (headache),[77] *Amasaya sula* (stomach pain),[71] *Antra sula* (pain in intestines), *vrikka sula* (kidney pain),[78] *Arso vyadha* (painful haemorrhoids),[69] etc. *Vijaya* (*Cannabis sativa*) is claimed to be *Rasayana* (Rejuvenating)[79] and *Sarva-rogaghni* (panacea)[80] which can also alleviate psychological disorders like *Arishad varga* (six nemeses of emotional balance). *Sattva* (goodness)[10] is the purest quality of *Vijaya* (*Cannabis sativa*) which is among the three primary attributes of mind said to be required for homeostasis in the neuronal impulses that balances all the physiological functions in the body. *Vyavayi guna* (fast diffusing quality)[9] is the specific property of *Vijaya* (*Cannabis sativa*) which first spreads or circulates quickly throughout the body to exert its action then undergoes *paka* (digestion) and *Yogavahi guna* (synergism)[10] contributes to the enhanced effects of the ingredients used in the processing

of Cannabis leaves. In vitro and in vivo research done gives a preliminary insight of Cannabis in modulating immune system, as a bronchodilator and in stopping the entry, replication of SARS-CoV-2.[36-52]

The base of the formulation Cow-Ghee itself enhances *Ojas* (immune booster),[33] conductive to *Rasa dhatu* (blood plasma) and *Sukra dhatu* (tissues of reproductive system)[81] commonly consumed for its properties viz- *Jwaraghna* (antipyretic), *Dipana* (appetiser),[33] *Bala* (strength promoting), *Cakshushya* (wholesome for eyes), *Visha hara* (removes toxins from body).[32] Ghee in general has *Swarya* (Voice promoting), *Ayushya* (longevity), *Vayahsthapana* (anti-ageing) properties and acts as *Rakshoghna* (ward off various infectious micro-organisms).[82] Ghee contains a short chain fatty acid called Butyric acid which modulates the differentiation of T-cells in the body thus strengthening the immune system.[83-84] It involves in epigenetic regulation of gene expression through the inhibition of histone deacetylase (HDAC) exerting anti-inflammatory and neuro-protective activity.[85-86] Vitamin-A in Cow-Ghee is involved in the homeostasis of bone marrow tissue by binding to retinoic acid receptor (RAR) in the bone marrow cells nucleus.[87] Vitamin-A has an important role in formation of epithelial and mucous membranes which are the first line of defence against microbes which invade GI-tract, genitourinary and respiratory tissues.[88] Vitamin-E in Cow-Ghee is a fat soluble antioxidant. [89-90] Both Vitamins A, E take part in differentiation, maturation and functions of immune components.

Cow-Milk added during the preparation process is a form of emulsion having Carbohydrates, proteins, sugars, vitamins, minerals, etc. Specifically Cow-Milk is said to be *Anabhishyandi*, that doesn't increase any slimy secretions in the internal channels of body, hence assist in smooth passage for the active ingredients without any blockage.[34] Cow-Milk is indicated for *Jwara* (fevers), *Swasa* (dyspnoea, shortness of breath), *Kasa* (cough), *Kshata-kshina* (emaciation due to ailments especially affecting chest), *Srama* (tiredness or fatigue), etc,[91] which are the common symptoms of Covid-19. Milk in general has attributes like *Dipana* (appetiser), *Sotha hara* (anti-inflammatory), *Sukra Dosha hara* (heals deranged *Sukra dhatu*)[92] that are key qualities to modulate deranged immunity. Cow-Milk contains fat soluble Vitamins A, D, E which are essential for development of body and immune system. Vitamin-D role is beyond skeletal tissue and calcium homeostasis, as its receptors are expressed on immune cells.[93-94] Contains minerals like calcium, potassium, magnesium, sodium, etc that are crucial for structural organisation of different tissues.[95]

Ojas (immunity) is also known as *Bala* (vitality) whose levels in the body is determined by the factors viz. *Sahaja* (naturally or innate immunity), *Kalaja* (acquired immunity) and *Yuktikrita* (kind of passive immunity). As per *Chakrapani* commentary *Yuktikrita* means intake of Ghee, *Rasayana* (rejuvenative) medication & healthy lifestyle like proper exercise, relaxation, etc, which improves *Ojas* (immunity).[96] To begin with, correcting of deranged immunity (or reversal of auto-immune condition) should be the primary objective before going for boosting or enhancing the immune system, as increasing the deranged immunity only aggravates suffering. Concept of vitiation of *Ojas* (deranged immunity) has been described in Ayurveda in three stages viz. *Visramsa* (dislodgement from its place), *Vyapat* (change in natural virtues i.e. contaminated) and *Kshaya* (diminution). Treatment of vitiated *Ojas* as per *Dalhana* commentary are *Rasayana* (rejuvenative), *Vajikarana* (aphrodisiac) therapies or/and *Bala-apyayana* (therapies that increasing immunity).[97] All of the ingredients in *Vijaya Ghrita* formulation are having *Rasayana* (rejuvenative), *Vajikarana* (aphrodisiac) properties that helps in both *Sodhana* (cleansing) and *Vardhana* (enhancing the quantity) of *Ojas*.

We should also purify *Sukra dhatu* as *Ojas* is produced from the former. Dual purification will ensure the purity (natural course) of already existing *Ojas* or *Bala* (immune components) and subsequent production from pure *Sukra dhatu*. Vitiation of *Sukra dhatu* primarily needs treatment with *Madhura-Tikta rasa* (sweet-bitter taste) dominant herbs.[55] In the present formulation, Ghee has a unique quality *Samskarasya anuvartanat* by virtue of which it assimilates the qualities of other herbs infused along without losing its own characteristics.[98] So, in the process of infusion *Tikta rasa* attribute[11] in *Vijaya* (Cannabis sativa) and *Madhura rasa* of Cow-Milk[34] are incorporated into Cow-Ghee which is having *Madhura rasa*[32] that makes *Vijaya Ghrita* a *Madhura-Tikta rasa* dominant medication and additionally *Tikshna guna* (sharp attribute)[72] of *Vijaya* (Cannabis sativa) is useful in quick purification of *Sukra dhatu* which in turn produce pure *Ojas* (immunity).

Sneha kalpana (traditional Ayurvedic method of Ghee/Oil infusion) has a precise methodology of preparation to incorporate hydrophilic (polar), lipophilic (non-polar) and amphiphilic compounds of the herbs added, which was shown by chromatography and HPTLC analysis specifying *Sneha paka* (medicated Ghee/Oil infusion) is an emulsion and can be correlated to liposomal drug delivery having greater absorption of herbal compounds through lipid bilayer and other membranes of target tissues.[99-100] Moreover phytocompounds in infused *Sneha paka* (medicated Ghee/Oil) move across the BBB (blood brain barrier) effortlessly by simple diffusion.[101] *Vijaya* (*Cannabis sativa* Linn.) used for infusion in Cow-Ghee in the present formulation has polar compounds like flavonoids, non-polar compounds Viz- terpenes and cannabinoids that are incorporated in the Cow-Ghee work collectively to produce an entourage effects that makes *Vijaya Ghrita* a good powerful remedy to fight against such viruses.

Psychological imbalance also affects immunity negatively[102-103] like in stress which triggers the release of hormones like Cortisol, a glucocorticoid steroid which weakens immune responses.[104-105] All the ingredients of *Vijaya Ghrita* formulation are having a special property called *Medhya* (brain tonic or nootropic)[6,82,106,107] which can reduce stress levels and maintain psychological homeostasis. Moreover these are potent appetisers[6,92,108] which can quickly correct the metabolism of impaired digestion and anorexia, the root cause in most of the diseases leading to complications said by *Acharya Vagbhata* (*Rogah Sarve api mandagnou*).[109] Sleep and immunity are bi-directionally linked as stimulation of immune system alters sleep pattern and sleep-wake cycle, the most prominent manifestation of the circadian rhythm has regulatory influence on immune functions like the proliferation, migration of immune components.[110-111] Proper and timely Sleep is one of the basic supportive pillars of life (*Upastambha*) that provides *Pushti* (nourishment), *Bala* (immunity), *Vrshata* (virility), *Ayusha* (longevity) as per Ayurveda.[112-113] Intake of *Ksheera* (Milk) and *Sneha dravya* (unctuous substances) like *Ghrita* (clarified butter/ Ghee) cures insomnia as per Ayurveda.[114] Also one of the main indication of *Vijaya* (*Cannabis sativa*) is Insomnia[6] which provides sound sleep in dose dependant manner. Regular intake of Milk and Ghee is a good vitalizing therapy for improving health mentioned in *Acara rasayana* (customary conduct for rejuvenation).[115] Present formulation is a blend of Milk and Ghee procured from *Desi* Cow which is considered as best for rejuvenation and immune modulation which can be used as a restorative medicine.

CONCLUSION

Improving the quality and quantum of immunity is an alternate parallel line of treatment helpful for Covid-19 patients, also beneficial as prophylactic and in post-Covid care. *Vijaya Ghrita*, an Ayurvedic Cannabis formulation best fits in all aspects as a potent immune modulator and for symptomatic relief from majority of Covid-19 disease features. Further research should explore this theorem in controlled pre-clinical & clinical trials.

Acknowledgements:- Nil
Financial Assistant:- Nil
Conflict Of Interest:- Nil

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How to cite this article: Ram G.S "Immune Modulating Theorem Of Vijaya Ghrita, A Fast Acting Ayurvedic Cannabis Formulation For Treating Covid-19 Disease Symptoms IRJAY.[online]2021;4(12);115-124.
Available from: https://irjay.com;
Doi:-https://doi.org/10.47223/IRJAY.2021.41218

Table-1. Research articles on Cannabis related to immune modulation, lung tissues and Covid-19.

S.No.	Type of research	Gist of Scientific Articles	Published year
1.	Pilot clinical trial	0.2 mg THC and 0.1 mg salbutamol in a standard metered aerosol produced similar bronchodilation when recorded after 1 hour of administration to ten asthmatic patients.	1976[36]
2.	Pilot clinical trial	0.1 mg THC in a standard metered aerosol gave optimal bronchodilation and there was an increase in both PEFR and FEV1 with no side effects and irritation in 5 asthmatic female patients.	1978[37]
3.	Pilot clinical trial	Double blind experimental studies on different Cannabinoids concluded 20 mg delta-9 THC and 75 mg delta-8 THC have acute bronchodilator activity along with different levels of tachycardia and high (intoxication).	1984[38]
4.	In vitro	CBD (Cannabidiol) and THC (Δ9-tetrahydrocannabinol) prevented hydroperoxide-induced oxidative damage and glutamate neurotoxicity.	1998[39]
5.	Review	Evidence of Antioxidant and neuroprotective activity of Cannabinoids.	2000[40]
6.	In vitro	Agonists at CB1 receptors inhibit EFS induced cholinergic contraction in human bronchi.	2014[41]
7.	Review	Explained the theorem of bronchodilation by THC (tetrahydrocannabinol) through CB1 receptors.	2018[42]
8.	Review	Summarising Immunomodulatory and neuroprotective effects of CBD (Cannabidiol) in experiments of *in vivo* and *in vitro*.	2020[43]
9.	Review	Sum up of anti-inflammatory and immunomodulatory properties of CBD (Cannabidiol).	2020[44]
10.	Pre clinical	THC (Δ9-tetrahydrocannabinol) at the dose of 20mg/kg i.p for first dose and 10mg/kg i.p for 2nd and 3rd dose with a time gap of 24 hours each modulated regulatory T-cells and decreased the pro-inflammatory cytokines of ARDS that was induced by SEB (Staphylococcal enterotoxin B).	2020[45]
11.	Review	CBD (cannabidiol) through the activation of CB2 receptors present in immune components acts as anti-inflammatory.	2020[46]
12.	Review	CBD (Cannabidiol) down-regulates ACE2 (angiotensin converting 2) and TMPRSS2 (transmembrane serine protease 2) enzymes main entries for SARS-CoV2 invasion. CBD exerts wide range of anti-inflammatory and immune modulator effects by acting on various receptors viz- PPARγ, 5-HT1A, adenosine A2A and TRP channels.	2020[47]
13.	In vitro	High CBD extracts down-regulates ACE2 (angiotensin converting 2) gene expression which is the gateway to SARS-CoV2 entry into host cells. Also the effect of extracts varied with cannabinoids and terpenes ratio, the entourage effect.	2020[48]
14.	Review	CB2 receptor activation can modulate immune responces and decrease the cytokine storm.	2020[49]
15.	Review	Cannabinoid receptors activation decreases cytokine storm. Also can downregulate ACE-2 receptor, TMPRSS2 protein expression which can stop the entry of SARS-CoV-2 and halt its replication respectively.	2021[50]
16.	Review	Cannabinoids by immune modulation decrease the pro-inflammatory cytokines like IL6 and increase anti-inflammatory cytokines like IL10.	2021[51]
17.	In vitro	Cannabis compounds Viz. CBD, CBG and THCV exhibited anti-inflammatory activity in COVID-19-related inflammation in lung epithelial cells and pro-inflammatory activity in macrophages	2021[52]