

Cannabis and its Effects on the Immune System

An extract from Cannabis: A General Survey of its Harmful Effects

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Since crude cannabis often contains various species of pathogenic fungi and bacteria it is important to establish the effects of cannabis smoking on the immune system.

The immune system exhibits a complex array of responses. Innate responses involve macrophages, important in engulfing and destroying foreign matter and natural killer cells, morphologically like lymphocytes, they bind to target cells and insert destructive granules into them.

Acquired immunity consists of lymphocytes.

B cells are responsible for the production of antibodies in “humoral immunity”. T cells carry out “cell-mediated immunity”. Activated T-lymphocytes act as cytotoxic cells and/or release substances which activate monocytes (the forerunners of macrophages) and macrophages.

Early research into the immune system was documented in the 1981/82 WHO Report into the adverse effects of cannabis.

Experimental animals consistently produced evidence that THC or marijuana administered parenterally or by inhalation resulted in immunological defects in mice and rats, rats being the more sensitive (Munson and Fehr 1982). These defects included decreased antibody responses and reduced lymphocyte proliferation. The cell-mediated immune suppression in mice was measured by a reduced response to bacteria, skin grafts and foreign cells, it also decreased lymphocyte proliferation. These results were obtained by THC doses which produced very little behaviour effects in the mice. However Smith and others in 1978 suggested that cannabinoids other than THC may contribute to the immunosuppressive effects. Rosenkrantz in 1976, experimenting on rats found that THC significantly inhibits humoral (related to the production of antibodies) and cell-mediated (dependent on the presence of activated T-lymphocytes) immunity in the immune response of rats in a dose-related manner. A similar response was obtained by marijuana smoke from an automatic inhaler (controlled by THC-absent smoke). Doses equivalent to human consumption were used.

At that time Munson and Fehr found the evidence as to whether THC or marijuana can perturb monocyte or macrophage function to be mixed. It appeared that the effects were more pronounced if the cannabinoids were given in the early phase of antibody production (Luthra et al 1980) and were even more pronounced in young animals (Pruess and Lefkowitz 1978). Also up till 1981/82 there was no definite proof of immune dysfunction in human users of cannabis. Evidence was very contradictory (Munson and Fehr 1982). They had looked at the numbers and functions of T and B-lymphocytes and macrophages. Serum immunoglobulin levels had also been investigated.

One study reported that the phagocytic ability of polymorphonuclear white blood cells was impaired (Petersen et al 1975) and another that there were biochemical and ultrastructural changes in the white blood cells of chronic hashish users (Stefanis and Issidorides 1976, Issidorides 1979).

Another approach to investigating a possible impairment of the immune system is to test the resistance of living organisms to infection. Cannabis-treated mice have shown a decreased resistance to infection by *Listeria monocytogenes* and Herpes simplex (Morahan and others 1979). In humans with dormant genital herpes, infections have been reactivated shortly after cannabis use (Juel-Jensen 1972). Other drugs which suppress the immune responses in mice also do the same in humans (WHO 1982).

A publication from the National Academy of Sciences, Institute of Medicine 1999, *Marijuana and Medicine: Assessing the Science Base*, gave an explanation of the problems encountered by human study researchers.

Blood leucocytes (white blood cells), isolated from people who have been smoking marijuana, used to evaluate the immune response in vitro almost always failed as the process involved high speed

centrifugation and washing. This removed the cannabinoids (Kaklamani et al 1978, Lau et al 1976, Rachelefsky et al 1976 and White et al 1975).

Blood leucocytes from non-users can be used to test the effect of THC on their ability to proliferate in response to stimulation *in vitro*. The problem here is that marijuana smoke consists of many distinct cannabinoids, not just THC. At least one of the others, CBN (cannabinol) has greater activity on the immune system than on the CNS (Central Nervous System) (Herring and others 1998).

Another approach is to study human-derived cell lines. These lines can be treated with cannabis *in vitro* to test the responses to various stimuli. However subsequent cells may not be the same as the original one, eg not have the same number of cannabis receptors.

The late eighties saw a re-surgence in research on cannabis and the immune system, probably prompted by the spread of AIDS.

RH Schwartz in an article in *The Journal of Hospital and Community Psychiatry* 1987 wrote that marijuana use is a factor in preparing the ground for HIV infection.

In 1988 Hamadeh and his associates warned that, "Invasive *Aspergillus* (a fungus) has become a significant cause of death in immuno-suppressed patients. Physicians should be aware of this potentially lethal complication of marijuana use in compromised hosts such as patients with AIDS or malignancies". Serious invasive fungal infections as a result of cannabis contamination have been reported among immunocompromised individuals including some with AIDS (Denning et al 1991).

In the same year, 1988, Tindall and others said that HIV positive marijuana smokers have an increased incidence of bacterial pneumonia compared to non-marijuana smokers, and added that marijuana smoking increases the progression to full-blown AIDS in HIV positive persons.

The fact that genital warts do not respond to systemic recombinant interferon alfa-2 treatment during cannabis consumption was discovered by Gross and others in 1991, and in 1994, Caiaffa and colleagues confirmed Tindall's findings that marijuana smoking increases the incidence of bacterial pneumonias in AIDS patients.

A more recent study discovered that THC suppresses the immune function and enhances HIV replication in the hu PBL-SCID mouse. Exposure to THC *in vivo* can suppress the immune function, increase HIV co-receptor expression and act as a co-factor to significantly enhance HIV replication (Roth et al 2005).

Some hospital patients who had smoked 12 marijuana cigarettes a day for 4 days were found to have decreased antibody production in one type (IgG), Two other types of antibody were normal (IgA and IgM), and IgE was actually elevated (Nahas et al 1991).

Human mononuclear phagocyte cultures were treated with THC *in vitro*. There was a suppression of phagocyte function and also the spreading ability of macrophages. A metabolite of THC, 11-OH-THC, was found to reduce natural killer cell activity (Specter and Lantz 1991).

Cabral and others in 1991 carried out some experiments on rhesus monkeys. They subjected them to marijuana smoke in various groups for over a year then gave them a 7-month rest period. "High-dose" animals were given one marijuana cigarette a day, "low-dose" ones 1 marijuana cigarette for two consecutive days at weekends. Both groups had altered morphology of alveolar macrophages and protein expression. The cell surfaces were irregular and there was increased vacuolarization. Hosts thus affected could be at increased risk of infection.

THC is able to interfere with the functioning of white blood cells taken from humans. Both neutrophils which fight bacterial infection and mononuclear cells of the immune system which fight viruses were suppressed by various concentrations of THC (Djeu et al, Watzl et al, 1991).

In 1992 Cabral and Vasquez discovered that THC inhibited extrinsic but not intrinsic anti-herpes activity in a dose-dependent manner. This means that THC had no effect on the capacity of macrophage-like cells to take up the virus and no replication of the virus occurred inside the

macrophage cells. However there was an inhibition of the macrophages to suppress viral replication in infected virus-susceptible cells. The action was reversible on removal of the drug.

In the same year Kaminski and others found that cannabis receptors CB2 on spleen cells, when activated by THC, suppress the system whereby a secondary messenger substance is released in the cells. This results in the suppressed system reducing the functioning of the spleen cells involved in the immune response.

Laboratory experiments exposing human and rodent cells to THC or other marijuana ingredients resulted in the inhibition of the normal disease-preventing reactions of many key types of immune cells (Adams and Martin 1996).

T-cell proliferation was found to be normal in a group of marijuana smokers but when examined more closely there was an increase in one sub-set and a decrease in another (Wallace et al 1988, Whitfield et al 1997). Intermittent disturbances in T and B cell function were found but the magnitude was small and other measures were frequently normal (Klein et al 1998).

Professor Guy Cabral of The Department of Microbiology and Immunology, Virginia Commonwealth University, in the last 20 years has written over 50 papers on the subject of marijuana and the immune system.

In 1998 Cabral and Pettit wrote a review paper on the subject of cannabis and immunity. "This substance (*THC*) has been shown to be immunosuppressive and to decrease host resistance to bacteria, protozoan and viral infections. Macrophages, T-lymphocytes and natural killer cells appear to be major targets of the immunosuppressive effects of THC. Definitive data which directly links marijuana use to increased susceptibility to infection in humans is currently unavailable, however the fact that current literature reports indicate that THC alters resistance to infection in vitro in a variety of experiments on animals supports the hypothesis that a similar effect occurs in humans.

Cabral wrote another review of the literature in 1999 in *Marijuana and Medicine* (Nahas and Latour eds). "Marijuana has been shown to decrease host resistance to bacterial, protozoan and viral infections in experimental animal models and in vitro systems. Recent immuno-epidemiological studies suggest that marijuana may also influence the outcome of viral infections in humans.....Delta-9-THC alters the functioning of an array of immune cells including lymphocytes, natural killer cells and macrophages, thereby affecting their capacity to exert anti-microbial activities....At sites such as the lung... THC may alter cellular membranes because of its highly lipophilic nature..., at sites distal to the lung, THC, at relatively low concentrations may exert its suppressive effects on immune cells by interacting with cannabinoid receptors CB1 and CB2".

A Columbia study in 1999 by Dr James Dobson found a control group smoking a single marijuana cigarette every other day for a year had a white blood cell count 39% below the normal. He said, "Marijuana can cause great harm".

Apoptosis is the key mechanism programmed by the genetic code which regulates the life and death of a cell. It is the "programmed cell death" of all mammalian cells. Apoptosis relates to the destruction of the DNA formation by the cell itself. Professor Gabriel Nahas, interviewed for an Italian newspaper, Italy Daily Roma in 2000 said the process accounted for the findings more than twenty-five years (1973) before of the damaging effects of marijuana and THC on lymphocytes. THC induces apoptosis of the cells. Because of the long-term storage of THC in body fat, the "death signals" from the THC remain in the body and act on the cells for weeks.

Cultures of immune cells from mice, splenocytes and peritoneal macrophages were treated with THC and the DNA fragmentation preceded membrane damage, indicating that THC induced apoptosis rather than necrosis (Zhu et al 1998).

Mice exposed to THC or related substances were more likely to develop bacterial infections and tumours than unexposed mice (Zhu et al 2000).

Friedman and his colleagues produced a review paper in 2003. It covered several drugs of abuse and their effects on immunomodulation. He said, "Recent studies of the effects of opiates or marijuana on

the immune system have demonstrated that they are receptor mediated, occurring both directly via specific receptors on immune cells and indirectly through similar receptors on cells of the nervous system.

Another deleterious effect of cannabis on the immune system was found by Tohyama and others in 2006. Cannabis can cause some white blood cells to lose the ability to migrate to sites of infection and inflammation. The cells seemed to lose their ability to develop a front/rear polarity needed to migrate to these sites.

The immune system has a part to play in the development of cancer through the activity of alveolar macrophages. The following paragraph is also included in my section on cannabis and cancer.

Alveolar macrophages protect the lungs from infection, they also kill tumour cells. Marijuana and tobacco smokers produce two or three times as many of these cells as non-smokers. The effects of smoking both being additive (Barbers et al 1987). The macrophages in both tobacco and marijuana smokers were larger and had more inclusions, probably due to the ingestion of smoke particles (Beals et al 1989). A more recent paper by Baldwin and others in 1997 found significant impairment of the macrophage cells of both tobacco and marijuana smokers. These cells have been shown to have cannabis receptors (Bouaboula et al 1993). Anti-tumour immunity depends on antigen-presenting dendritic cells being able to stimulate the proliferation of T lymphocytes that identify and destroy tumour cells. The in-vitro studies in which dendritic cells and T lymphocytes were incubated with or without THC, the THC suppressed the T cell proliferation in a dose-dependent manner (Roth et al 1997). Two earlier papers were written on this subject in 1975 by Petersen et al and Nahas et al. DNA alterations have been seen in the lymphocytes of pregnant marijuana smokers and their newborns. This study is particularly important as tobacco smokers were excluded (Ammenheuser et al 1998). Cannabis smoking also depressed pro-inflammatory cytokine production. Cytokines regulate macrophage function so this may account for the impairment of their ability to kill tumour cells (Baldwin et al 1997).

Low levels of THC inhibited the tumour necrosis factor, thereby weakening the killing activity of lymphocytes against tumour cells (Kusher et al 1994).

Zhu and colleagues in 2000 showed that THC suppresses host immune reactivity against lung cancer. In two different lung cancer models in mice, intermittent administration of THC led to accelerated growth of tumour implants. He said, "Our findings suggest that THC promotes tumour growth by inhibiting anti-tumour immunity by a CB2 receptor-mediated pathway".

Pacifici and others in 2003 found cannabis smokers had fewer natural immune-enhancing killer cells and lymphocytes and higher levels of a protein that may promote tumour growth called interleukin-10. These changes can dampen the immune system's responses to infection, increasing susceptibility to infection and promoting tumour growth.

"The inability of alveolar macrophages from habitual marijuana smokers without apparent disease to destroy fungus, bacteria and tumour cells, and to release pro-inflammatory cytokines, suggests that marijuana might be an immunosuppressant with clinically significant effects on host defence. Therefore the risks of smoking marijuana should be seriously weighed before recommending its use in any patient with pre-existing immune deficits – including AIDS patients, cancer patients, and those receiving immunosuppressive therapies (for example, transplant or cancer patients)" (National Academy of Sciences *Marijuana and Medicine* 1999).

There have been a few papers putting forward the idea that cannabinoids or their metabolites may prove useful in the treatment of some cancers.

The administration of THC and a synthetic cannabinoid agonist into the tumour induced a considerable regression of malignant gliomas in rats and in mice. No substantial neurotoxic effect was produced by the cannabinoid treatment in the conditions employed.

Two glioma cell lines in culture demonstrated that the cannabinoids signalled apoptosis in the cells. It was suggested that these results may provide the basis for a new therapeutic approach for the treatment of malignant gliomas (Galve-Roperph et al 2000).

A metabolite of THC is 11-COOH-THC, and ajulemic acid (AJA) is a synthetic analogue of it. In cell cultures AJA proved to be approximately one half as potent as THC in inhibiting tumour growth against a variety of tumour cell lines. However its effects lasted longer. The conclusion was that AJA produced significant anti-tumour activity and effected its actions primarily through CB2 receptors (Recht et al 2001).

Casanova and colleagues in 2001 showed that both CB1 and CB2 receptors are present in hair follicles and skin. The synthetic cannabinoid WIN55, 212-2 induced a decrease in the viability of several mouse skin cancer cell lines, non-cancer lines being unaffected. This occurred through the process of apoptosis. CB1 and CB2 receptors were involved.

Providing that purified single extracts of cannabinoids or synthetic equivalents are subjected to the rigorous clinical testing required by law, there should be no objection to these proposals. Crude cannabis is not a candidate for medical use.

Zhang et al in 2007 produced a paper showing that “the use of cannabinoids may place individuals at greater risk of the development and progression of Kaposi’s sarcoma. The herpes virus associated with the development of Kaposi’s sarcoma, KSHV, is needed but insufficient for its development. Marijuana was investigated for its effect on this disease. “Our results indicate that delta 9 THC can enhance KSHV infection and replication and foster KSHV-mediated endothelium transformation. Thus, use of cannabinoids may place individuals at greater risk for the development and progression of Kaposi’s sarcoma”.

Cannabis has been shown to modulate mitochondrial function and induce cell death in a paper in 2007 by Athanasiou and others. Time-lapse microscopy of human lung cancer (H460) cells showed that anandamide (AEA), THC and a synthetic cannabinoid (HU210) all caused morphological changes characteristic of apoptosis. All 3 ligands caused significant decreases in oxygen consumption and mitochondrial membrane potential in rat heart mitochondria. THC and HU210 significantly increased the production of hydrogen peroxide, AEA had no significant effect. Further evidence was obtained of the damaging effects on mitochondria (the structures in cells which produce energy).

In 2007 a paper by Eisenstein et al found that both THC and anandamide directly inhibit cells of the immune system via CB2 receptors.

A paper by Chao et al in 2008 found that recreational drug use does not adversely affect CD4 cell counts. They wrote, “We did not find any clinically meaningful associations, adverse or otherwise, between use of marijuana, cocaine, poppers, or amphetamines and T-cell counts and percentages in either HIV-uninfected or HIV-infected men”. However in their conclusion they added, “although the circulating numbers of CD4 and CD8 T cells do not appear to be significantly affected by use of these substances, these findings do not preclude the possibility that substance use may adversely affect the functional properties of T cells”.

Ishida and others in January 2008 found that chronic marijuana use may increase fibrosis for Hepatitis C patients. Between 2001 and 2004, 204 patients with hepatitis C were interviewed for risk factors associated with HCV and use of alcohol and cannabis. Virologic testing and liver biopsies were carried out. Current daily cannabis use increased the odds of moderate to severe fibrosis by nearly 7-fold. This study confirms an earlier French one of 2004 that came to the same conclusion of an increase in fibrosis in daily users.

A paper in February 2008 (Thomson et al) found that cannabis smoking may be a risk factor for periodontal disease, independent of tobacco use. The Dunedin NZ Longitudinal Study supplied the data for this research. Three groups were determined, no exposure to cannabis, 293(32.3%), some exposure, 428(47.4%) and high exposure, 182(20.2%) .The incidence of Combined Attachment Loss (CAL), between 26 and 32 years of age, in the none group was 6.5%, some exposure 11.2% and high exposure 23.6%. After controlling for tobacco use, sex, irregular use of dental services and dental plaque, the relative risk estimates of the highest group were 1.6 for having 1 or more sites with 4mm or greater with CAL, 3.1 for having 1 or more sites with 5mm or greater CAL and 2.2 for having CAL compared with the “none” group.

Hegde et al, 2010 found that THC suppresses the immune system by massively expanding the number of myeloid-derived suppressor cells (MDSC) both in vivo and in vitro. These cells in the immune system have only recently been discovered. These cells have been known to increase in cancer patients so they may suppress the immune system against cancer chemotherapy, actually promoting cancer growth. The lead author, Dr Prakash Nagarkatti concluded, 'Marijuana cannabinoids present us with a double-edged sword. On one hand due to their immuno-suppressive nature, they can cause increased susceptibility to cancer and infections. However, further research of these compounds could provide opportunities to treat a large number of clinical disorders where suppressing the immune system is actually beneficial'.

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