

Anti-inflammatory Cannabinoids without psycho-active side-effects

Opportunities for further development to a drug formulation

Introduction

More than 5000 years ago, the Chinese already used *Cannabis* for medical purposes. Since then, the plant and its products have been used successfully for a variety of diseases in many parts of the world. As with many other herbal medicinal products, its medical use gradually disappeared during the 20th century with the appearance of the synthetic medicines. Moreover, due to the recreational use of marijuana, which is illegal in most countries, the plant lost its credibility. However, during the last decades Cannabis started to find its way to patients with severe appetite suppression, weight loss, cachexia due to HIV infection, chronic pain, severe nausea and vomiting associated with cancer and its treatment, and to patients suffering from Multiple Sclerosis. The further development of Cannabis-based therapies is currently receiving considerable attention in the scientific community, where different university groups and consortia are active in this area.

Cannabis: issues and challenges

Despite the ongoing activities described above, there are a number of technical and medical challenges left open within the Cannabis arena that offer excellent business opportunities, These include:

- New formulations of Cannabis, preferably given via the oral route (or via inhalation) of known and standardised quality and with constant bioavailability.
- *Idem*, with proven less psycho-active (hallucinogenic) properties and similar or even higher therapeutic efficacy
- New indications for Cannabis preparations (dermal, intestinal) and the development of suitable formulations for this (dermal patch, cream or ointment, suppository)

Novel “acidic ? cannabinoids

TNO Pharma (Leiden and Zeist, the Netherlands), the mother company of Fytagoras, and Maripharm BV

(Rotterdam, the Netherlands) have discovered a group of Cannabinoids with potent anti-inflammatory and immuno-modulating properties. This achievement is based on the combination of a long-standing tradition in the selection, cultivation and application of Cannabis specifically

for medicinal use present within Maripharm, together with the unique expertise in genomics, metabolomics, and multivariate analysis of TNO. Our findings enable the development of a new generation of Cannabis preparations with fewer hallucinogenic side-effects and potent anti-inflammatory properties. Possible areas of indication include disease of skin and GI tract, chronic pain and diseases of bone and joints. The findings have been laid down in a patent claim, published August 2005 (WO2005072719, MEDICINAL ACIDIC CANNABINOIDS, published August 11th 2005).

Background of the invention

Unheated cannabis extract and THC-acid were found to be able inhibiting the tumour necrosis factor alpha (TNF- α) release from U937 macrophages and peripheral blood macrophages after stimulation with LPS in a dose -dependent manner. Furthermore, we demonstrated that THC-acid does not interact with the CB1 or CB2 receptors. In stead, we have found evidence for a completely new mechanism of action, based on the interaction with phosphatidylcholine specific phospholipase C (PC-PLC). Unheated cannabis extract and THC-acid inhibit the PC-PLC activity in a dose dependent manner. We have further investigated these findings in EAE mouse model. The EAE model is a well-accepted model for multiple sclerosis (MS). Unheated cannabis extract and THC-acid had positive effects on the clinical and histological signs of EAE. Possible other areas of indication include diseases of skin (dermatitis and psoriasis) and GI tract (inflammatory bowel disease), chronic pain, diseases of bone and joints (arthritis) and inflammation of the respiratory tract (Asthma and COPD).

REFERENCE (APPENDIX 1) :

Verhoeckx, Kitty C.M. *et al.*, Unheated Cannabis sativa extracts and its major compound THC-acid have potential immuno-modulating properties not mediated by CB1 and CB2 receptor coupled pathways. *International Immunopharmacology* 6 (2006) 656– 665.

Invention and claims

Our invention relates to an acidic cannabinoid for medical use and to a cannabis extract comprising an acidic cannabinoid. The extract may comprise one or more compounds selected from the group consisting of cannabidiolic acid (CBD-A), cannabidiol (CBD), cannabigerolic acid (CBGA), cannabigerol (CBG), cannabinolic acid (CBN-A) and cannabinol. The invention further relates to a method for preparing a preparation comprising extracting an acidic cannabinoid from cannabis.

Main claims (abbreviated)

- Extract for use as a medicament.

- Pharmaceutical preparation comprising at least one compound according to any one of the claims and a pharmaceutically acceptable carrier.
- Pharmaceutical preparation wherein the preparation is selected from the group consisting of tinctures, ointments, sprays, inhalants, powders, granules, suppositories, creams, tablets and capsules.
- Use of an acidic cannabinoid an extract or a preparation in the manufacture of a medicament for administration of the cannabinoid in acidic form to an animal, preferably a human.
- Use of an acidic cannabinoid, an extract, or a preparation in the manufacture of a medicament for relieving pain.
- Use of a acidic cannabinoid according in the manufacture of a medicament for suppression of an inflammatory response, preferably for suppressing release of a pro-inflammatory cytokine, in particular TNF- α and/or stimulating release of an anti-inflammatory cytokine, in particular interleukin-10.
- Use of an acidic cannabinoid in the manufacture of a medicament for treating a medical indication (disease) selected from the group consisting of infections, inflammations, autoimmune diseases and symptoms associated with a disease, preferably selected from the group consisting of multiple sclerosis, arthritis, AIDS, inflammatory bowel disease, Crohn's disease, inflammatory skin diseases (such as dermatitis, Psoriasis), encephalomyelitis and alleviated symptoms associated with cancer, anorexia, AIDS, spasticity, glaucoma and chronic pain.
- Method of treating an animal with an acidic cannabinoid or a preparation, which treatment comprises administering the acidic cannabinoid in acidic form.
- Method according wherein the cannabinoid is used to treat an animal, preferably a human, suffering from a disease selected from the group consisting of multiple sclerosis, arthritis, AIDS, inflammatory bowel disease and Crohn's disease.
- Method for manufacturing an preparation comprising an acidic optionally in the form of an extract or a pharmaceutical preparation comprising extracting the acidic cannabinoid from harvested parts of a plant, preferably cannabis, under conditions at which decarboxylation of the acidic cannabinoid is avoided.
- Method wherein said conditions involve extraction at a temperature of less than 95 C, preferably a temperature not exceeding about 25 C.
- Method wherein said conditions involve extraction at a temperature not exceeding about 4 C.

REFERENCE (APPENDIX 2) : WO2005072719, MEDICINAL ACIDIC CANNABINOIDS

Further development path

There are several possibilities for development of the cannabinoids and/or extracts to one or more pharmaceutical formulations, such being dependent on the indications and way of administration that is to be selected :

Options include for example:

- Formulation of unheated extract or THC-acid in an ointment or cream for inflammatory disorders of the skin (dermatitis, pruritis, allergic reactions)
- Formulation unheated extract or THC-acid in a rectal formulation against localised inflammatory disorders (proctitis, colitis)
- Alternatively : formulation in a controlled oral delivery form for IBD
- Formulation of THC-acid in an inhalatory preparation against pain

Business Options

Maripharm and TNO-APS/Fytagoras are seeking third parties to participate in the further development of pharmaceutical preparations based on THC-acid, “cold◆◆? extracts or other acidic cannabinoids for different applications. Options include full co-development / participation or via licensing in specific areas outside the scope of the development company. We will be happy to discuss any option with interested parties.

Appendix 1 : International Immunopharmacology 6 (2006) 656– 665.

Appendix 2 : patent claim WO2005072719, MEDICINAL ACIDIC CANNABINOIDS