**Δ⁹-tetrahydrocannabinolic acid A: a reliable marker for differentiating between the consumption of illegal cannabis products and legal, medical Δ⁹-THC**

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**ABSTRACT:** Δ⁹-Tetrahydrocannabinolic acid A (Δ⁹-THCA-A) is the biosynthetic precursor of Δ⁹-tetrahydrocannabinol (Δ⁹-THC) in plant material of cannabis sativa, without having psychoactive effects. Δ⁹-THCA-A is not contained in pharmaceutical Δ⁹-THC formulations. Thus, Δ⁹-THCA-A can serve as a marker for differentiating between the consumption of illegal cannabis products and legal fully synthetic Δ⁹-THC.

**Key Words: Cannabis, Δ⁹-tetrahydrocannabinol, Δ⁹-tetrahydrocannabinolic acid**

Cannabis is the most popular recreational drug globally. The resin of Cannabis plant contains more than 84 chemical compounds with psychoactive effects, known as cannabinoids, the most efficacious of which is Δ⁹-tetrahydrocannabinol (Δ⁹-THC). The biogenesis of Δ⁹-THC starts with olivetolic acid, that is produced in the plant from the condensation of hexanoyl-CoA with three molecules of malonyl-CoA. In the next step, olivetolic acid is alkylated to cannabigerolic acid, which is then converted to cannabidiolic acid. Cannabidiolic acid is the precursor of Δ⁹-tetrahydrocannabinolic acid A (Δ⁹-THCA-A or Δ⁹-THCA). Δ⁹-THCA-A is a non-psychoactive substance that is decarboxylated to Δ⁹-THC via heating, when cannabis products are smoked.

The therapeutic effects of Δ⁹-THC have been known since ancient times, when cannabis was used as a medicine for many different pathological conditions such as insomnia, headaches, gastrointestinal disorders and pain. Nowadays, the cultivation, possession and transfer of cannabis is illegal in most of the European countries and is convicted by law. On the other hand, medical Δ⁹-THC is provided, mainly in the U.S, to treat a range of diseases and the ensuing symptoms. Marinol® (U.S, Canada) is an oral drug containing fully synthetic Δ⁹-THC, known as dronabinol and is used to treat anorexia in people suffering from AIDS, and also to minimize nausea and vomiting associated with cancer therapy. Another popular pharmaceutical compound, used to treat spasticity and neuropathic pain associated with multiple sclerosis, is Sativex® (U.S, Europe, New Zealand). Sativex® is an oromucosal spray which contains nabiximols, a mixture of compounds derived from cannabis plant. The principal cannabinoid components of the drug are synthetic Δ⁹-THC and cannabidiol.

The high popularity of illegal cannabis and the use of legal fully synthetic Δ⁹-THC in recent years, demonstrated the need to find reliable markers in biological samples for differentiating between the consumption of illegal cannabis products and legal medication containing fully synthetic Δ⁹-THC.

Δ⁹-THCA-A could serve as a marker of illegal consumption of cannabis products if the substance is detected in biological samples of cannabis users. Δ⁹-THCA-A attracted scientists’ attention in recent years, as it is the precursor substance of natural Δ⁹-THC in plant material and is not contained in Marinol® or Sativex®. In 2005, it was shown that during smoking cannabis joint, Δ⁹-THCA-A is only partially converted to Δ⁹-THC and therefore it can be taken up by the consumer.

In 2007, Jung et al. detected Δ⁹-THCA-A in the urine and blood serum samples collected from police controls of drivers suspected for driving under the influence of drugs (DUID). Liquid chromatography tandem-mass spectrometry (LC-MS/MS) was used for Δ⁹-THCA-A determination. Δ⁹-THCA-A was detected in the urine and blood serum samples of cannabis users in concentrations of 10.8 ng/ml in urine and 14.8 ng/ml in serum. The concentration of Δ⁹-THC was higher than the concentration of Δ⁹-THCA-A in most serum samples. In the above paper, Δ⁹-THCAOOH-D3 was used as internal standard (IS) because the isotopically labeled Δ⁹-THCA-A was not commercially available.

In 2012, Roth et al. succeeded to synthesize deuterated Δ⁹-THCA-A. Metabolism studies of Δ⁹-THCA-A in rats showed that the main metabolites of THC-A were formed in close analogy to Δ⁹-THC metabolism and twelve metabolites were identified.

In 2013, Brabanter N. et al. developed a fast method for quantification of Δ⁹-THCA-A in urine using microwave-accelerated derivatization and gas chromatography–triple quadrupole mass spectrometry. Their method could quantify Δ⁹-THCA-A in 30 min, using only 1 mL of urine.

In 2013, Raikos N. et al. analyzed fifty eight authentic whole blood and the respective plasma samples collected from drivers suspected for driving under the influence of cannabis, using LC-MS/MS. Δ⁹-THCA-A concentrations ranged from 1.0 to 496 ng/mL in blood samples and from 1.4 to 824 ng/mL in plasma samples. Δ⁹-THC was present in all blood samples with levels ranging from 0.7 to 51 ng/mL. The plasma:blood partition coefficient had a mean value of 1.7.

In 2010, Auwarter et al. concluded that Δ⁹-THCA-A can be incorporated in hair only by external contamination e.g. by condensate of smoked cannabis material and not by blood.

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or sweat and Δ⁹-THCA-A could be a valuable marker for external cannabinoid contamination of hair. In conclusion, Δ⁹-THCA-A can be detected in blood and urine samples of cannabis consumers and this detection in biological fluids may serve as a marker for differentiating between the intake of legally prescribed Δ⁹-THC medication and illegal cannabis products. However, the knowledge about its usefulness in forensic cases is very limited and further research is needed.

Δ⁹-τετραϋδροκανναβινολικό οξύ Α: ένας αξιόπιστος δείκτης για τη διάκριση μεταξύ της χρήσης παράνομων προϊόντων της κάνναβης και της λήψης φαρμακευτικής Δ⁹-THC.

Δέξεις Κλειδιά: Κάνναβη, Δ⁹-τετραϋδροκανναβινολή, Δ⁹-τετραϋδροκανναβινολικό οξύ Α
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