The current status of *Cannabis sativa* L. therapeutic potential

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Cannabis sativa L. Cannabaceae is, according to currently relevant taxonomy, the only species of genus *Cannabis* L. The history of its exploitation dates 5000 years BC, during which the co-existence of two types of *Cannabis sp*. could be observed. Glandular trichomes are the most important structures of *C. sativa* regarding the production of secondary metabolites of interest. Plants predominantly containing glandular trichomes are producing more resin and are used, or better to say abused, for their psychoactive effects. On the other hand, the plants predominantly containing non-glandular trichomes are being cultivated for production of fiber, as well as for food production. Although containing some common secondary metabolites, such as phenolics, flavonoids and alkaloids, *C. sativa* is of particular interest because of its resin, which is highly abundant in terpenoids and cannabinoids. Cannabinoids, commonly termed as phytocannabinoids, are terpenophenolic compounds derived from cannabigerolic acid. More than 100 cannabinoids have been isolated from *C. sativa*, but only ten of them have been studied in detail, of which tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) are attracting the most of research interest. It is important to highlight that THC and CBD do not exist in fresh plant material, but are being derived after harvest (or heat treatment) by decarboxylation of corresponding acidic forms – tetrahydrocannabinolic (THCA) and cannabidiolic (CBDA) acids. Furthermore, CBN is an oxidation product of THC and is primarly of interest in the area of forensics. The crucial difference between THC and CBD lays in their psychoactive potential. *Cannabis* plants containing resin rich in THC are consumed for their psychoactive effect, while CBD-rich plants (containing low amounts of THC) are not psychoactive, and are termed as hemp (or industrial hemp). The importance of phytocannabinoids for human physiology has been better understood after discovery of endocannabinoid system and corresponding cannabinoid receptors (CB1 and CB2). Namely, it was concluded that endocannabinoids regulate a number of processes in immunological and central nervous system. Therefore, phytocannabinoids as CB1 and CB2 agonists have the potential to interfere with these interactions (activation of potassium- and inhibition of calcium-dependent channels, regulation of GABA and glutamate release, activation of adenyl cyclase and extracellular kinases) which could be used in treatment of various pathological conditions. The previously stated was scientifically confirmed since anti-inflammatory, analgesic, anticonvulsive, neuroprotective, antipsychotic and immunosuppressive effects were reported for THC, CBD, cannabichromene (CBC), cannabigerolic acid (CBGA), etc. The successfully conducted clinical studies have shown benefits of CBD application in specific forms of child epilepsy – Lennox - Gastaut and Dravet syndrome. Furthermore, THC has been proved as effective supportive therapy in cancer and HIV-patients, as well as in patients with multiple sclerosis (MS). Although, a large number of studies reported cytotoxic and antiproliferative effects of THC, it must be stated that these *in vitro* studies were found as clinically irrelevant. However, the clinical significance of THC as partial agonist of CB1 and CB2 is reflected through exhibiting antiemetic effect and increasing the pain threshold, acting as anticonvulsive and increasing the patients' appetite, which is of particular importance in pathological conditions resulting with cachexia. The adverse effects of phytocannabinoids are mostly limited to THC-related psychoactive effects, while mode of interactions relate to increasing the P-glycoprotein expression and additive effects with drugs exhibiting similar pharmacological effect.

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