**Aldose Reductase Inhibitors from Cannabis sativa L. Standardized Extracts**

1)A. Smeriglio 2)E. M. Galati 3)S. Giofrè 4)M.T. Monforte 5)N. Cicero 6)V. D'Angelo 7)G. Grassi 8)C. Circosta

*Dept. of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, 98168 Messina, Italy*

Aldose reductase (ALR2) is the first enzyme of the polyol pathway that catalyzes the reduction of glucose to sorbitol. The intracellular accumulation of sorbitol, due to increased aldose reductase activity at high blood glucose levels, such as those occurring in diabetes, has been implicated in the development of various secondary complications of diabetes such as neuropathy, nefropathy, retinopaty, and cataracts, which practically are not controlled by insulin. The aldose reductase inhibitors (ARIs) are capable of preventing the reduction of glucose to sorbitol and reduce complications of diabetes (Kinoshita, 1990; Bhatnagar and Srivastava, 1992). The synthetic ARIs are often associated with deleterious side effects and poor penetration of target tissues such as nerve and retina (Pfeifer et al. 1997). The natural sources containing compounds with aldose reductase inhibitory activity, expecially medicinal and edible plants, could be non-toxic and then could be useful for prevention and therapy of diabetic complications. Cannabis sativa L. (Cannabaceae) has been an important source of food, fibre, dietary oil and medicine for thousands of years in Europe, Asia and Africa (Prociuk et al., 2008). It is characterized by the presence of terpenophenolic compounds, known as cannabinoids. The well-known psychotropic effects of Δ9-THC, have greatly limited therapeutic use of Cannabis. However, the presence in Cannabis sativa of non-psychotropic cannabinoids could be promising for its possible use in therapy, free of the side psychotropic effects. Non-psychotropic phytocannabinoids exert multiple pharmacological effects with therapeutic potential in many diseases and cannabidiol has also been proven useful for possible complications of diabetes (Izzo et al., 2009; Rajesh et al., 2007). In this study, was investigated in vitro inhibition of aldose reductase activity by standardized extracts and isolated cannabinoid–rich fractions from Cannabis sativa L. cannabidiol (CBD)- or cannabigerol (CBG)-type. The extracts of cannabis CBD- and CBG-type were subjected to MPLC yielding four cannabinoid-rich fractions. An HPLC method was performed for the simultaneous identification and quantification of both acidic and neutral cannabinoids and a spectroscopic (1H NMR, GC-MS) analysis has been carried out to characterize extracts and fractions. The extracts showed significant dose-dependent aldose reductase inhibitory activity (>70%). The inhibitory activity of the fractions was greater for isolated acidic cannabinoid-rich fraction. Docking studies were performed to evaluate the interaction of cannabinoids with the active site of ALR2. Comparative molecular docking results have shown a higher stability of the ALR2-cannabinoid acids complex than the other inhibitors, explaining their highest ALR2 inhibitory activity.

Kinoshita, J. (1990). H. Exp. Eye Res. 50, 567–573.

Bhatnagar, A. and Srivastava, S. K. (1992). Biochem. Med. Metab. Biol. 48, 91–121.

Pfeifer, M. A., Schumer, M. P. and Gelber, D. A. (1997). Diabetes 46, S82–89.

Izzo, A.A.; Borrelli, F.; Capasso, R.; Di Marzo, V.; and Mechoulam, R. (2009). Trend Pharmacol. Sci. 30 (10), 515-527.

Prociuk, M.A.; Edel, A.L.; Richard, M.N.; et al. (2008). Can J Physiol Pharmacol 86, 153–159.

Rajesh, M.; Mukhopadhyay, P.; Bátkai, S.; Haskó, G.; Liaudet, L.; Drel, V.R.; Obrosova, I.G.; Pacher, P. (2007). Am J Physiol Heart Circ. Physiol. 293(1), H610-619.