LEAF EXTRACT OF MORUS ALBA, A COMPONENT OF LOPIGLIK, REDUCES THE EXPRESSION OF PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9) IN HEPG2 CELL LINE

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Genetic, observational and, more recently, clinical studies have firmly established that Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) represents an effective pharmacological target for controlling hypercholesterolemia and associated cardiovascular diseases. The current available therapies for blocking PCSK9 are represented by monoclonal antibodies, i.e. evolocumab and alirocumab, which very efficiently reduce the low-density lipoprotein cholesterol (LDL-C) both in monotherapy and in combination to statins. The additive effect of therapies anti PCSK9 and statins is a result of a well-established basic molecular mechanism that involved the sterol regulatory element-binding protein (SREBP) transcription factor. Indeed, statins, by inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, induce the SREBP transcription activity, which, in turn, drives the expression of the LDL receptor (LDLR) and PCSK9 that counteracts the upregulation of the LDLR by inducing its degradation. Thus, the inhibition of PCSK9 improves the effect of statins on the expression of the LDLR. In the present study, we investigated the effect of different components of a novel nutraceutical LopiGLIK® with hypocholesterolemic properties, i.e. berberine, red yeast rice (RYR) and leaf-extract of Morus alba (MA) on PCSK9 in HepG2 cell line. As previously reported berberine (100µM) and RYR (50µg/ml) showed opposite effect on PCSK9 levels (-89.3±6.9% and +76.5±26.8% for berberine and RYR, respectively). These effects were also confirmed by measuring the PCSK9 released into the cultured media by ELISA assay (-68.0%±10.7% and +30.1±14.6% for berberine and RYR, respectively). The effect of MA on PCSK9 was then measured at different concentrations (0.25÷1.0 mg/ml). The incubation of HepG2 cells for 24h with MA, determined a concentration-dependent inhibition of mRNA PCSK9, with a maximal reduction of 52.5±8.3% at 1 mg/ml. The same concentration of MA also reduced the levels of PCSK9 in the conditioned media (-46.6±12.8%). Interestingly, LopiGLIK did not alter the PCSK9 plasma levels in 23 dyslipidemic subjects, after 4 weeks of treatment (312.9±69.4 ng/ml vs 334.8±103.5 ng/ml, at baseline and after 4 weeks, respectively). In conclusion, both MA and berberine significantly reduced the PCSK9 levels, an inhibitory effect that counteracts the induction of monacolin K present in the RYR. Their combination in the nutraceutical LopiGLIK® could, therefore, help to elicit an efficient hypocholesterolemic action.

This study was partially supported by Akademy Pharma.