TOPICAL ADMINISTRATION OF RESVERATROL AS PRE- AND ANTINEOPLASTIC AGENT

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Resveratrol (trans-3,5,4'-trihydroxystilbene) is a phytoalexin naturally produced by some plants. *In vitro* studies demonstrated its efficacy in inhibiting the growth of many tumor cell lines, by stopping their replication in S phase and inducing apoptosis. Resveratrol efficacy in reducing activity and expression of NF-kB, cyclooxigenase 2 and metalloproteinases 9 has been shown *in vivo* in rodents, thus confirming its potential antineoplastic application. Clinical use of resveratrol has nevertheless been limited by the rapid metabolic inactivation it goes through after systemic administration.
The aim of our work has been the evaluation of antineoplastic activity of resveratrol after topic administration, which preserves it from metabolic inactivation, on preneoplastic and neoplastic lesions. Local administration of the drug is possible only in certain anatomical districts. Oral squamous cell carcinomas (OSCC) are an important therapeutical possibility. Besides of being unresponsive to most of the available antineoplastic drugs, they develop through a series of preneoplastic lesions that can easily be reached for topical application of the drug.
In vivo experimentation has been driven in an animal model where cancer has been induced by topical administration of 7,12-dimethylbenz[a]anthracene (DMBA). Though neoplastic induction in animal models is actually dismissed, for this particular cancer histotypes it represents an important method, considering the risk factors characterising the clinical evolution of this tumor, such as smoke and alcohol. These lesions are very similar to the human ones, both histologically and genetically, therefore making this model particularly reliable.
We induce OSCC in hamster cheek pouches by painting them three times a week with DMBA. From the beginning of chemical induction, a solution of resveratrol is applied two times a week on the cheek pouches. Animals are checked weekly and lesion evolution is closely monitored. After 16 weeks of treatment animals are sacrificed and tissues removed and processed for histological analysis. Results show that topical applications of resveratrol decrease tumor number both at the ninth week and at the end of treatment and, particularly, it decreases the number of exophytic lesions. Moreover, it decreases the number of white lesions at the beginning of the treatment and, globally, topical application of resveratrol are efficient at decreasing, all along the treatment period, the tumor score, a parameter which considers both the number and the gravity of lesions. In conclusion, we consider that topical application of resveratrol might be considered as a possible treatment for neoplastic and preneoplastic lesions of oral cavity.