Our Dermatology Online

Case Letter

The "neue welle" of meristem cells of blossoms, roots or fruits and buds of whichever botanical "vagary" in cosmetic may be risky for Human Health

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Sir,

When for the first time Carl Wilhelm von Nägeli in 1858 proposed the employ of meristem cells for pharmacological usage in his book Beiträge zur Wissenschaftlichen Botanik ("Contributions to Scientific Botany"), the culture of these stem cells appeared to represent a great revolution in the progress or Science and Art of Medicine.

Since the second post war the culture of whichever stem cells were a mirage and a dream but at the end of 60ies of XX century the production of stem cells began routinaire even if very complex and expensive.

Thanks to the specialization of technology, nowadays the large scale production of meristem cells of herbs and plants is more rapid and cheap!

And its usage in cosmetics has being growing more and more exploited and explored as their employ and insertion in cosmetic formulas and one assists to a very great enthusiasm and a sort of fetishism and morbid rabidity.

Nowaday the market is awash with cosmetic items that boast of this Renaissance and Promise of Eternal Youth, but after an accurate scrutiny of the eventuality of the conjunctival absorption by these meristem cells (especially of Capsicum annuum or futescens) one may observe a great risk for Human Health, as the conjunctival way of whichever drug administration is the fastest than all the other pharmacokinetic routes.

In effect Ocular drug delivery has been a major challenge to pharmacologists and drug delivery scientists due to its unique anatomy and physiology. Static barriers (different layers of cornea, sclera, and retina including blood aqueous and blood–retinal barriers), dynamic barriers (choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution), and efflux pumps in conjunction pose a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment. Identification of influx transporters on various ocular tissues and designing a transporter-targeted delivery of a parent drug has gathered momentum in recent years. Parallelly, colloidal dosage forms such as nanoparticles, nanomicelles, liposomes, and biocosmetic microemulsions have been widely explored to overcome various static and dynamic barriers. Novel drug delivery strategies such as bioadhesive gels and fibrin sealant-based approaches were developed to sustain drug levels at the target site. Designing noninvasive sustained drug delivery systems and exploring the feasibility of topical application to deliver drugs to the posterior segment may drastically improve drug delivery in the years to come. Current developments in the field of ophthalmic drug delivery promise a significant improvement in overcoming the challenges posed by various anterior and posterior segment diseases.

Eye is a sensitive organ [1] and protected from foreign materials by its curved architecture, compartmental organization, impermeable epithelium, tear secretion and ocular drainage pathways to clear any foreign

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object [2-4]. Conventional drug delivery systems such as eye drops, suspensions and ointments are frequently indicated for ocular diseases albeit with several disadvantages. Conversely, new approaches such as nano/microparticle, nanosuspension, nano/microemulsion, liposomes, nanomicelles, and dendrimers may overcome the above drawbacks of conventional systems [5]. However, most important tools to develop novel ocular delivery systems are to study ocular pharmacokinetics models. In general, the objectives of pharmacokinetics studies involve the study of time and concentration relationships of the administered drugs [6].

Capsicum-derived ingredients function as skin-conditioning agents--miscellaneous, external analgesics, flavoring agents, or fragrance components in cosmetics. These ingredients are used in manifold cosmetic products at concentrations as high as 5%. Cosmetic-grade material may be extracted using hexane, ethanol, or vegetable oil and contain the full range of phytocompounds that are found in the Capsicum annuum or Capsicum frutescens plant (aka red chiles), including Capsaicin. Aflatoxin and N-nitroso compounds (N-nitrosodimethylamine and N-nitrosopyrrolidine) have been detected as contaminants, that are superabundant in the meristem cells. The ultraviolet (UV) absorption spectrum for Capsicum Annuum Fruit Extract indicates a small peak at approximately 275 nm, and a gradual increase in absorbance, beginning at approximately 400 nm. Capsicum and paprika are generally recognized as safe by the U.S. Food and Drug Administration for use in food. Hexane, chloroform, and ethyl acetate extracts of Capsicum Frutescens Fruit at 200 mg/kg resulted in death of all mice. In a short-term inhalation toxicity study using rats, no difference was found between vehicle control and a 7% Capsicum Oleoresin solution. In a 4-week feeding study, red chilli (Capsicum annuum) in the diet at concentrations up to 10% was relatively nontoxic in groups of male mice. In an 8-week feeding study using rats, intestinal exfoliation, cytoplasmic fatty vacuolation and centrilobular necrosis of hepatocytes, and aggregation of lymphocytes in the portal areas were seen at 10% Capsicum Frutescens Fruit, but not 2%. Rats fed 0.5 g/kg day-1 crude Capsicum Fruit Extract for 60 days exhibited no significant gross pathology at necropsy, but slight hyperemia of the liver and reddening of the gastric mucosa were observed. Weanling rats fed basal diets supplemented with whole red pepper at concentrations up to 5.0% for up to 8 weeks had no pathology of the large intestines, livers, and kidneys, but destruction of the taste buds and keratinization and erosion of the gastrointestinal (GI) tract were noted in groups fed 0.5% to 5.0% red pepper. The results of 9-and 12-month extension of this study showed normal large intestines and kidneys. In rabbits fed Capsicum Annuum Powder at 5 mg/kg day-1 in the diet daily for 12 months damage to the liver and spleen was noted. A rabbit skin irritation test of Capsicum Annuum Fruit Extract at concentrations ranging from 0.1% to 1.0% produced no irritation, but Capsicum Frutescens Fruit Extract induced concentration-dependent (at 25 to 500 microg/ml) cytotoxicity in a human buccal mucosa fibroblast cell line. An ethanol extract of red chili was mutagenic in Salmonella typhimurium TA98, but not in TA100, or in Escherichia coli. Other genotoxicity assays gave a similar pattern of mixed results. Adenocarcinoma of the abdomen was observed in 7/20 mice fed 100 mg red chilies per day for 12 months; no tumors were seen in control animals. Neoplastic changes in the liver and intestinal tumors were observed in rats fed red chili powder at 80 mg/kg day-1 for 30 days, intestinal and colon tumors were seen in rats fed red chili powder and 1,2-dimethyl hydrazine, but no tumors were observed in controls. In another study in rats, however, red chile pepper in the diet at the same dose decreased the number of tumors seen with 1,2-dimethylhydrazine. Other feeding studies evaluated the effect of red chili peppers on the incidence of stomach tumors produced by N-methyl-N'-nitro-N-nitrosoguanidine, finding that red pepper had a promoting effect. Capsicum Frutescens Fruit Extract promoted the carcinogenic effect of methyl(acetoxymethyl)nitrosamine (carcinogen) or benzene hexachloride (hepatocarcinogen) in inbred male and female Balb/c mice dosed orally (tongue application). Clinical findings include symptoms of cough, sneezing, and runny nose in chili factory workers. Human respiratory responses to Capsicum Oleoresin spray include burning of the throat, wheezing, dry cough, shortness of breath, gagging, gasping, inability to breathe or speak, and, rarely, cyanosis, apnea, and respiratory arrest. A trade name mixture containing 1% to 5% Capsicum Frutescens Fruit Extract induced very slight erythema in 1 of 10 volunteers patch tested for 48 h. Capsicum Frutescens Fruit Extract at 0.025% in a repeated-insult patch test using 103 subjects resulted in no clinically meaningful irritation or allergic contact dermatitis. One epidemiological study indicated that chili pepper consumption may be a strong risk factor for gastric

cancer in populations with high intakes of chili pepper; however, other studies did not find this association. Capsaicin functions as an external analgesic, a fragrance ingredient, and as a skin-conditioning agent--miscellaneous in cosmetic products, but is not in current use. Capsaicin is not generally recognized as safe and effective by the U.S. Food and Drug Administration for fever blister and cold sore treatment, but is considered to be safe and effective as an external analgesic counterirritant. Ingested Capsaicin is rapidly absorbed from the stomach and small intestine in animal studies. Subcutaneous injection of Capsaicin in rats resulted in a rise in the blood concentration, reaching a maximum at 5 h; the highest tissue concentrations were in the kidney and lowest in the liver. In vitro percutaneous absorption of Capsaicin has been demonstrated in human, rat, mouse, rabbit, and pig skin. Enhancement of the skin permeation of naproxen (nonsteroidal anti-inflammatory agent) in the presence of Capsaicin has also been demonstrated. Pharmacological and physiological studies demonstrated that Capsaicin, which contains a vanillyl moiety, produces its sensory effects by activating a Ca2 +-permeable ion channel on sensory neurons. Capsaicin is a known activator of vanilloid receptor 1. Capsaicin-induced stimulation of prostaglandin biosynthesis has been shown using bull seminal vesicles and rheumatoid arthritis synoviocytes. Capsaicin inhibits protein synthesis in Vero kidney cells and human neuroblastoma SHSY-5Y cells in vitro, and inhibits growth of E. coli, Pseudomonas solanacearum, and Bacillus subtilis bacterial cultures, but not Saccharomyces cerevisiae. Oral LD50 values as low as 161.2 mg/kg (rats) and 118.8 mg/kg (mice) have been reported for Capsaicin in acute oral toxicity studies, with hemorrhage of the gastric fundus observed in some of the animals that died. Intravenous, intraperitoneal, and subcutaneous LD50 values were lower. In subchronic oral toxicity studies using mice, Capsaicin produced statistically significant differences in the growth rate and liver/body weight increases. Capsaicin is an ocular irritant in mice, rats, and rabbits. Dose-related edema was observed in animals receiving Capsaicin injections into the hindpaw (rats) or application to the ear (mice). In guinea pigs, dinitrochlorobenzene contact dermatitis was enhanced in the presence of Capsaicin, injected subcutaneously, whereas dermal application inhibited sensitization in mice. Immune system effects have been observed in neonatal rats injected subcutaneously with Capsaicin. Capsaicin produced mixed results in S. typhimurium micronucleus and sister-chromatid exchange genotoxicity assays. Positive results for Capsaicin were reported in DNA damage assays. Carcinogenic, cocarcinogenic, anticarcinogenic, antitumorigenic, tumor promotion, and anti-tumor promotion effects of Capsaicin have been reported in animal studies. Except for a significant reduction in crown-rump length in day 18 rats injected subcutaneously with Capsaicin (50 mg/kg) on gestation days 14, 16, 18, or 20, no reproductive or developmental toxicity was noted. In pregnant mice dosed subcutaneously with Capsaicin, depletion of substance P in the spinal cord and peripheral nerves of pregnant females and fetuses was noted. In clinical tests, nerve degeneration of intracutaneous nerve fibers and a decrease in pain sensation induced by heat and mechanical stimuli were evident in subjects injected intradermally with Capsaicin. An increase in mean inspiratory flow was reported for eight normal subjects who inhaled nebulized 10(-7) M Capsaicin. The results of provocative and predictive tests involving human subjects indicated that Capsaicin is a skin irritant. Overall, studies suggested that these ingredients can be irritating at low concentrations. Although the genotoxicity, carcinogenicity, and tumor promotion potential of Capsaicin have been demonstrated, so have opposite effects. Skin irritation and other tumor-promoting effects of Capsaicin appear to be mediated through interaction with the same vanilloid receptor. Given this mechanism of action and the observation that many tumor promoters are irritating to the skin, the Panel considered it likely that a potent tumor promoter may also be a moderate to severe skin irritant. Thus, a limitation on Capsaicin content that would significantly reduce its skin irritation potential is expected to, in effect, lessen any concerns relating to tumor promotion potential. Because Capsaicin enhanced the penetration of an anti-inflammatory agent through human skin, the Panel recommends that care should be exercised in using ingredients that contain Capsaicin in cosmetic products. The Panel advised industry that the total polychlorinated biphenyl (PCB)/pesticide contamination should be limited to not more than 40 ppm, with not more than 10 ppm for any specific residue, and agreed on the following limitations for other impurities: arsenic (3 mg/kg max), heavy metals (0.002% max), and lead (5 mg/kg max). Industry was also advised that aflatoxin should not be present in these ingredients (the Panel adopted < or =15 ppb as corresponding to "negative" aflatoxin content), and that ingredients derived from Capsicum

annuum and Capsicum Frutescens Plant species should not be used in products where N-nitroso compounds may be formed.

Time is the only judge apt to solve this dilemma, hitherto many are the buyers who trust on these novelties, purchasing them on line, but during the Pharmacological History many have been the disasters eye contour cosmetics have induced in women or men. as Kohl, Kajal, Al-Kahal, Surma, Tiro, Tozali, or Kwalli used profusely in Arabian countries and Afghanistan.

It is sufficient to wait and pay attention to the evolution: que sera sera.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

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