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Essential oils as novel human skin penetration enhancers

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Summary

Essential oils were evaluated as penetration enhancers towards 5-fluorouracil using excised human skin. Eucalyptus and chenopodium were found to be very effective, causing a near 30-fold increase in the drug permeability coefficient. Ylang ylang was mildly effective (8-fold increase) and anise had little activity (3-fold increase).

Transdermal delivery of drugs promises many advantages over oral or intravenous administration, but human skin provides an effective barrier to the permeation of most drugs. The principal barrier to topical drug delivery is the stratum corneum, the outer most layer of the skin comprising keratin-rich cells embedded in multiple lipid bilayers. In recent years much interest has been focused on methods of increasing stratum corneum permeability, and one approach is the use of penetration enhancers (or accelerants). These agents partition into, and interact with, the stratum corneum constituents to induce a temporary, reversible increase in skin permeability. We have investigated the penetration enhancing activities of some essential oils towards the permeation of 5-fluorouracil (5-FU), chosen as a model polar penetrant, in excised human skin.

The essential oils selected were chenopodium, eucalyptus, anise and ylang ylang. Oil of chenopodium has been used as an effective anthelmintic, and contains approx. 70% ascaridole, as well as *p*-cymene, α-terpinene and l-limonene. Eucalyptus oil has been employed in ointments as a topical counter-irritant and, together with menthol, as an inhalation. Its chief constituent is 1,8-cineole (approx. 80%) although it also contains α-pinene and small quantities of other terpenes such as phellandrene. Anise oil provides approx. 85% anethole and is an established flavouring agent used in the manufacture of liqueurs and dentifrices. Oil of ylang ylang yields geraniol and linalool esters of benzoic and acetic acids, together with *p*-cresol methyl ether and other terpenes. It is employed as a delicate fragrance agent and has recently found use in aromatherapy. Due to the popularity of these essential oils their toxicities are well documented (Opdyke, 1974–1976), and are relatively low compared to most synthetic penetration enhancers.

The activities of the essential oils were evaluated using excised human epidermal membranes prepared by a heat-separation technique (Kligman and Christophers, 1963; Goodman and Barry, 1988). The skin samples were fully hydrated and

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placed in stainless-steel diffusion cells, comprising stationary donor and flow through receptor compartments, mounted on an automated diffusion system (Akhter et al., 1984). Aliquots of 150 μl of a saturated, aqueous radiolabelled 5-FU solution were placed in the donor compartments and samples of receptor solution were collected periodically and the drug determined by liquid scintillation counting. At pseudo steady-state diffusion, the permeability coefficient (K_p) of the drug in the tissue was evaluated. The drug was then washed from the donor compartments and replaced with samples of the essential oils. After a 12 h treatment period the oils were washed from the donor compartments and replaced with the drug solution; the permeability coefficient at steady state was re-evaluated. An enhancement ratio (ER) may be used to define the activities of the oils;

$$ER = \frac{K_p \text{ after accelerant treatment}}{K_p \text{ before accelerant treatment}}$$

The enhancement ratios reported are mean values, from a minimum of five replicates, using 12 different tissue samples. Human skin permeability shows inter-sample variations; the experimental technique employed each piece of tissue as its own control thus minimising errors due to this phenomenon. Expressing the activities of the oils as the mean of individual enhancement ratios given a more accurate estimation of penetration enhancement than a simple ratio of the mean membrane permeability coefficients before and after accelerant treatment.

The oils clearly increased drug permeation across the skin as illustrated in Table 1.

The most effective oils were eucalyptus and chenopodium containing primarily 1,8-cineole and ascaridole, respectively. Both these chemicals are polar oxygen-bridged terpenes, 1,8-cineole being a cyclic ether and ascaridole a cyclic peroxide. Oil of ylang ylang shows less penetration enhancing activity towards the polar drug 5-FU, with an enhancement ratio of approx. 8. This oil contains oxygen-linked molecules with its terpene ester composition. The least effective essential oil, anise (ER approx. 3), contains primarily anethole, a chemical containing a methoxybenzene structure.

TABLE 1

The mean permeability coefficients (K_p) and enhancement ratios, with standard error of the mean, of 5-FU in human epidermal membranes at 32 ± 1 °C before and after treatment with an essential oil

Essential oil	K_p (cm/h) ($\times 10^5$)		Enhancement ratio
	Initial (control)	Treated	
Anise	2.30 ± 0.34	6.33 ± 0.50	2.8 ± 0.6
Ylang ylang	3.79 ± 1.25	29.6 ± 9.90	7.8 ± 2.6
Chenopodium	4.33 ± 1.32	93.5 ± 29.1	33 ± 8.0
Eucalyptus	2.09 ± 0.42	69.3 ± 13.4	34 ± 8.9

The importance of these chemical configurations in determining the penetration enhancing activities of these oils is, however, yet to be proven.

Some essential oils and their terpene constituents have recently been investigated as potential penetration enhancers. Eucalyptus oil and camphor increase the total flux of nicotine permeating excised hairless mouse skin (Nuwayser et al., 1988), although this animal is a suspect model for human in vitro skin (Bond and Barry, 1988). Terpineol and acetyl terpineol, prepared as the acetone extract of cardamon seeds, enhance in vitro diffusion of prednisolone through hairless mouse skin (Yamahara et al., 1989), and the percutaneous absorption of indomethacin has been promoted by the use of limonene and related compounds in rats (Okabe et al., 1989).

Clearly, further studies are required to isolate the active constituents of these essential oils, and investigations of the accelerant activities of the wide variety of naturally occuring terpenes and terpenoids may prove profitable. This study has shown that the essential oils may offer a large and useful selection of relatively safe penetration enhancers to aid topical drug delivery.

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