Abstract
If vitiligo involves most of the body, it might be easier to depigment the normal remaining skin rather than to attempt repigmentation. We reviewed the literature to date regarding available therapies for depigmenting the normal skin in vitiligo universalis. Our review revealed that the threshold regarding what percentage of body surface area qualifies as depigmentation is variable among practitioners. Monobenzyl ether of hydroquinone (MBEH) is the most widely used depigmenting agent and has few side-effects. Tretinoin in combination with MBEH is able to speed depigmentation of the skin. Monomethylether of hydroquinone has also been used successfully for depigmentation. Eighty-eight per cent phenol is also effective in depigmenting the skin but its application on large areas is toxic for liver and kidney. Different types of lasers are also available to destruct the melanocytes selectively, but this technique can be painful and expensive. Cryotherapy is a cheap depigmenting therapy but, because of scarring risk, it should only be used by experienced dermatologists. No trials have compared the efficacy of the above-mentioned well-established depigmentation agents/techniques. Certain drugs such as imatinib, imiquimod and diphencyprone, which are used to treat other diseases, caused depigmentation as a side-effect. Some depigmentation agents used for branding cattle can also serve as topical depigmentation agents. In conclusion, comparative clinical trials are needed to compare the efficacy of various depigmentation agents/techniques. In particular, topical imatinib, imiquimod and diphencyprone may be considered as potential depigmenting agents, which require further investigation. This review revealed that MBEH is safe and effective depigmenting agent.

Keywords
88% phenol, cryotherapy, depigmentation therapies, diphencyprone, imatinib, imiquimod, lasers, monobenzyl ether of hydroquinone, monomethylether of hydroquinone

Conflict of interest
None declared.
often embarrassed by the remaining normally pigmented patches on their exposed areas and wish to be depigmented rather than attempt repigmentation.

**Threshold for depigmentation**

Generally, depigmentation therapy can be considered if vitiligo affects more than 60% to 80% of the body. A recent survey, however, showed variation among dermatologists, where 32% of dermatologists were in favour of depigmentation when vitiligo affects more than 75% of the body while 42% dermatologists were in favour of depigmentation when vitiligo affects more than 50% of the body. Expert consensus recommends that patient selection is important in depigmentation treatment. In general, depigmentation is undertaken only when the patient has more than 50% pigment loss in their skin because of vitiligo, or when the depigmentation is extensive in the cosmetically sensitive areas of the hands and face. Depigmentation is not recommended for children.

In patients with extensive areas of depigmentation and/or disfiguring lesions on the face who do not respond to repigmentation therapies (e.g., phototherapy), depigmentation can be useful because complete repigmentation may never occur even after long periods of phototherapy. Sometimes subtotal repigmentation may be achieved after patients undergo 150–200 sessions of psoralen plus ultraviolet A (PUVA) therapy with or without adjuvant therapy but there is always a possibility of depigmentation after cessation of PUVA therapy. Therefore, complete depigmentation rather than repigmentation therapy is recommended by many investigators in case of vitiligo universalis. During and upon completion of the depigmentation therapy, patients are permanently at risk for acquiring sunburn. Patients should therefore be advised to minimize sun exposure and to apply broad-spectrum sunscreens because recurrence of the pigment is also observed within a few weeks of discontinuing successful depigmentation therapy on sun-exposed sites. Oakley reported that repigmentation occurred within a few weeks of discontinuing successful depigmentation therapy with monobenzyl ether of hydroquinone (MBEH) in a patient with extensive vitiligo. Patients undertaking depigmentation therapy should be warned about repigmentation.

We aimed to systematically review the published scientific literature regarding different depigmenting agents such as depigmenting creams, lasers, cryotherapy, and systemic drugs, to compare their advantages and disadvantages for treatment of vitiligo universalis. Moreover, we aim to shed light on additional potential depigmentation agents. We searched databases including MEDLINE/PubMed, Embase and Google Scholar for vitiligo, leucoderma, depigmentation therapies and vitiligo universalis. We found no controlled studies that compared the efficacy or safety of various depigmenting agents.

**Agents for depigmentation**

The ideal depigmenting compound should have a potent, rapid and selective effect on melanocytes, carry no short- or long-term side-effects and lead to permanent removal of pigment. There are several well-established as well as potential depigmenting agents, and certain chemical agents used for branding cattle, that can cause depigmentation as a side-effect (Table 1).

**Monobenzyl ether of hydroquinone**

Monobenzyl ether of hydroquinone is the mainstay of depigmentation therapy. It is also referred to as monobenzene or by its chemical name, p-(benzyloxy) phenol. MBEH is a topical product used for the treatment of pigmentary disorders such as melasma, solar lentigines and pigmented nevus. Arndt and Fitzpatrick applied MBEH (10–20%) to the normally pigmented areas surrounding vitiligo lesions to induce complete skin depigmentation, to achieve uniform skin tone. Ultimately 90–95% of patients were fully bleached after the application of 20% MBEH cream. If vitiligo has been stable for years, a longer duration of therapy and higher concentration of MBEH may be required. The process of depigmentation requires twice daily application of cream and allotment of time each day. In general, depigmentation of particular site can require 5–12 months of therapy. If depigmentation does not occur over the course of 3–4 months of application of 20% MBEH then concentration of MBEH can be increased upto 40% but MBEH concentration greater than 40% is not recommended.

In an animal study, MBEH produced significant cutaneous depigmentation of guinea pig skin and its oral administration to laboratory animals induced visually recognizable hypomelanosis in the hair. MBEH is known to interfere with melanocyte activity. Recently, Hariharan et al. reported that MBEH can induce cell death because of disintegration of cellular membranes and release of cellular contents, without activating the caspase cascade or DNA fragmentation. Therefore, the death pathway is non-apoptotic. Release of high mobility group box-1 protein by MBEH-treated human melanocytes and ultra-structural features, such as disruption of the plasma membrane and the nuclear membrane, further confirmed a necrotic death pathway mediated by MBEH. Riley postulated that MBEH diffuses into melanosomes of pigment cells where the enzyme tyrosinase converts it to toxic species such as quinones, which react with essential cellular macromolecules such as proteins and DNA and cause melanocyte death.

**Table 1 Established and potential depigmenting agents**

<table>
<thead>
<tr>
<th>Established agents</th>
<th>Potential agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monobenzyl ether of hydroquinone (MBEH)</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Monomethyl ether of hydroquinone</td>
<td>Imiquimod</td>
</tr>
<tr>
<td>88% phenol solution</td>
<td>Diphenycyprone</td>
</tr>
<tr>
<td>Laser</td>
<td>Catechol</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>Hydroquinone bis (2-hydroxyethyl) ether</td>
</tr>
<tr>
<td>4-Ethoxyphenol</td>
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</tbody>
</table>

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irreversible and is associated histologically with loss of melanosomes and, eventually, loss of melanocytes.4,5

In many institutions worldwide, depigmentation therapy consists of the application of a bleaching agent containing MBEH.28,58–59 Application of MBEH is reserved for induction of complete depigmentation in severely affected vitiligo patients who cannot or do not choose to repigment, as well as those who wish to be universally amelanotic.39,40

All-trans retinoic acid (RA), a vitamin A derivative primarily utilized for the treatment of acne, is shown to serve as a weak depigmenting agent when used for several weeks.41 However, use of this drug in combination with MBEH resulted in depigmenting activity in black guinea pigs.22 This combination induced significant depigmentation within 4–8 weeks.41 Nair et al. proposed that RA might enhance the skin penetration of depigmenting agents.43 Thus, RA increases the susceptibility of melanocytes to hydroquinone and 4-hydroxyanisole through the impairment of glutathione-dependent defense mechanisms of melanocytes44 and reducing melanogenesis activity in viable melanocytes.55

Side-effects

Although the use of MBEH may lead to a satisfying degree of depigmentation in most patients, some disadvantages such as skin irritation, contact dermatitis and ocular side-effects have also been reported.27,40,66 In addition, exogenous ochronosis is also reported as a potential complication after application of MBEH in many cases.47,48 In some cases MBEH resistance16 and recurrence of the pigment were also observed18 because of intense sun exposure.49 Therefore, the use of MBEH has been restricted in the Netherlands, since 1990.13 However, MBEH remains the only drug that the Food and Drug Administration, USA has approved for depigmentation therapy of advanced vitiligo.50,51

4-methoxyphenol or mequinol

This compound is a phenol derivative and also known as ‘5-hydroxyanisole’ or ‘monomethylether of hydroquinone’. The compound has been shown to have melanocyte-toxic properties that are comparable with those of MBEH.31,52 The effectiveness of 4-methoxyphenol (MP) was significantly correlated with the duration of use of the cream; the longer the cream was used, the better the results.13 However, compared with MBEH cream, a disadvantage of 4-MP was the longer time prior to the onset of visible depigmentation (between 4 and 12 months), whereas it was previously reported that depigmentation with MBEH may already be evident after 1 month.28 Recently, a combination product of 2% 4-hydroxyanisole (Mequinol) and 0.01% tretinoin was tested in a double-blind multicentre study and was found to significantly improve solar lentigines and related hyperpigmented lesions of the face and hands after a twice-daily application of up to 24 weeks.53

Melanocytes in the hair follicles may also be affected by 4-MP in a dose-response fashion, but because of their deeper localization, these melanocytes in comparison with epidermal melanocytes are less susceptible to the compound.32

Side-effects

Mild burning or itching, irregular leucoderma and skin irritation were reported with 4-MP.56,54 Patients should be advised that pigment may return and protection from sunlight is necessary.13

88% phenol solution

This solution is inexpensive and applied topically for chemical peeling. Protein coagulation is observed in the epidermis immediately after application of 88% phenol solution.53 It can penetrate deep into the tissue, down to upper reticular dermis.58 All phenol compounds have toxicity towards melanocytes. Transient or definite hypopigmentation after application of phenol is due to the development of a melanocytic incapacity to normally synthesize melanin.57 On the other hand, other depigmenting agents, such as hydroquinone and MBEH, destruct the melanocytes. It is reported that hydroquinone causes depigmentation because of decrease tyrosinase activity by 90% and reversible inhibition of cellular metabolism by affecting both DNA and RNA synthesis of melanocytes.58 Additionally, unlike hydroquinone, MBEH almost always causes a nearby irreversible depigmentation of skin. It has been suggested that the mechanism of depigmentation by MBEH involves selective melanocytic destruction through free radical formation and competitive inhibition of the tyrosinase enzyme system.59 Eighty-eight per cent phenol solutions can be considered as a therapeutic option to eliminate residual normally pigmented areas in patients with generalized vitiligo.

Side-effects

Generally, 88% phenol solution does not produce any complications in experienced hands. However, sometimes 88% phenol solution produces complications such as non-aesthetic scar formation, dyschromia and development of herpetiform eczema. High-dose phenol usage is toxic, so it should not be applied over large areas.60 Phenol exerts marked corrosive action on any tissue it contacts when ingested, inhaled or brought into contact with the skin. Its cellular uptake is both rapid and passive because of its lipophilic character and signs of systemic toxicity develop soon after exposure. Phenol’s main target organs are liver, kidney, respiratory and cardiovascular systems. Cardiovascular shock, cardiac arrhythmias and bradycardia, as well as metabolic acidosis have been reported within 6 h of skin peeling procedures with phenol.61 Re-pigmentation may occur if patients do not protect themselves properly from ultraviolet radiation.62

Laser

Depigmentation with strong bleaching creams, such as MBEH or MP, is very effective but several side-effects were also reported.63 It usually takes 10 months or more for a complete loss of pigment to occur, with the possibility of only partial depigmentation and
a relatively high failure rate, as it is reported that success rate of MBEH for depigmentation is 69%. It was also observed that repigmentation on sun-exposed sites may also occur after complete depigmentation by MBEH. Unfortunately, in some cases, permanent depigmentation is not achieved and irregul-derma and severe irritation of the skin have been reported. The laser apparatus is another form of depigmenting therapy for vitiligo. Depigmentation therapy using lasers can be applied in cases where patients do not respond well to the depigmentation cream or in areas, especially the face, where rapid depigmentation is required.

Lasers have proven to be highly effective in selectively targeting melanocytes for destruction, thus causing depigmentation. The Q-switched ruby (QSR, 694 nm) and alexandrite (755 nm) lasers are known to induce selective photothermolysis of pigmented lesions because their wavelengths are between 600 nm and 800 nm, which are absorbed more easily by melanin than by haemoglobin. Light emitted by both lasers is well absorbed by melanin.

The QSR laser selectively targets melanosomes and destroys melanocytes and keratinocytes. Because of the QSR laser effects, the more tan skin is, the more therapeutic the effects become. Tanning can induce activation of melanocytes in normal pigmented areas and these activated melanocytes are the target of selective photothermolysis performed with pigment-specific lasers. Therefore, QSR laser therapy after tanning can induce permanent damage in activated melanocyte-containing structures. There are many advantages to depigmentation therapy with QSR laser: the therapeutic effects are fast and safe; the duration of treatment is short; and the area to be depigmented can be large, as compared with depigmentation performed using a bleaching agent. An additional advantage of the QSR laser is that its beam reduces the risk of scar formation on the skin.

The Q-switched alexandrite (QSA) laser has shown efficacy in treating both naturally occurring pigmented lesions and exogenous pigment. The QSA therapy is safe, simple and effective in treating recalcitrant pigmentation after depigmentation therapy in vitiligo patients. The QSA laser is advantageous over the QSR laser because it has a faster pulse frequency, which allows for more rapid therapy. In addition, it also has a higher wavelength of 755 nm, as compared with the 694 nm QSR laser, which facilitates greater tissue penetration and improves results.

Other potential Q-switched lasers that can selectively destruct melanocytes include neodimum:yttrium aluminium garnet (Nd:YAG) laser (1064 nm) and the frequency-doubled Nd:YAG laser (532 nm). Anderson and Parrish postulated that selective photothermolysis could be predicted by choosing appropriate wavelength, pulse duration and pulse energy for a particular target. Melanin absorbs light of shorter wavelengths more efficiently within the range from 250 nm to 1200 nm. Therefore, melanin can be selectively destroyed by 532 nm wavelengths because this wavelength is strongly absorbed by melanin resulting destruction of melanocytes, thus causing depigmentation.

Side-effects
The main disadvantage of this therapy is that sometimes local anaesthesia is required because it may be painful to the patients. Therefore, this treatment is only possible in the clinic, rendering it an expensive therapy. The QSR laser therapy may fail in permanently removing pigmented patches and after several months of treatment both epidermal repigmentation and an increased number of dermal macrophages have been observed.

Cryotherapy
Cryotherapy is suitable for very small lesions and cannot be utilized if the surface area of pigmented lesions is more than a few centimetres. Cryotherapy has been suggested to depigment MBEH-resistant skin. Cryosurgery is melanocytotoxic and can easily kill melanocytes. Cryosurgery was used to remove normally pigmented patches in patients with universal vitiligo. The melanocytes in non-segmental vitiligo are particularly prone to mechanical and thermal destruction due to isomorphic Koebner phenomenon, whereby local trauma to the skin (e.g. rubbing) can induce depigmented patches. Although Koebner phenomenon is more pronounced in progressive rather than stable vitiligo but still the melanocytes in stable vitiligo are much more vulnerable to thermal and mechanical damage than melanocytes in normal individuals. As cryotherapy is commonly performed utilizing liquid nitrogen, which is the most effective cryogen for clinical use. Irreversible damage in treated tissue occurs because of intracellular ice formation. Therefore, melanocytes are more sensitive to cryodamage in comparison with other cutaneous cell components such as keratinocytes, fibroblasts and endothelial cells. The degree of damage depends on the rate of cooling and minimum temperature achieved. Inflammation develops during the 24 h after treatment, further contributing to destruction of lesion through immunologically mediated mechanisms. Mild freezing leads to a dermoeipidermal separation, which is useful in treating epidermal lesions.

Cryotherapy has numerous advantages over other modalities. Preparation time is short and treatment requires no other expensive supplies or injectable anaesthesia. In addition, the risk of infection is low and wound care is minimal. This technique is used to remove many melanocytic lesions including simple or solar lentigines, junctional nevi and cafe-au-lait spots without causing permanent damage to other cell structures or scarring in vitiligo patients.

This method is simple, easy to perform, safe, efficacious and cost effective. Therefore, it may be superior to other medical and surgical methods. Depigmentation developed by cryotherapy is permanent, not scar forming, if performed by experienced dermatologists. The technique yields excellent cosmetic results.

Side-effects
If cryotherapy is performed aggressively, it can lead to permanent scarring. Cryotherapy should be used by experienced person delicately to avoid side-effects.
**Potential depigmenting agents**

**Imatinib**
Imatinib is used for the treatment of leukaemia. Vitiligo-like depigmentation of the skin was observed as a side-effect of treatment with this drug in several patients with chronic myeloid leukaemia (CML). Skin hypo-pigmentation was noted in five patients with CML who were treated with imatinib mesylate.80 Imatinib mesylate is a tyrosine kinase inhibitor and selectively inhibits the constitutive activity of this enzyme, resulting in decreased pigmentation of the skin. After patients begin receiving imatinib mesylate, hypo-pigmentation can be observed within 12 weeks.81

**Side-effects**
The side-effects of imatinib mesylate (Table 3) are peri-orbital oedema, fluid retention, diarrhoea and myelosuppression.82 In addition, a number of dermatological side-effects have been documented, such as follicular mucinosis, erythroderma and lichenoid eruption. Imatinib mesylate can also induce local or generalized hyper-pigmentation.83

**Imiquimod**
Imiquimod (1-(2-methylpropyl)-1H-imidzo[4,5-c]quinolin-4-amine), a low molecular weight imidazoquinolinamines, has potent antiviral and antitumour properties and approved from Food and Drug Administration, USA84 for the topical treatment of external anogenital warts caused by human papillomavirus (HPV) and for the skin cancers such as superficial basal cell carcinoma (BCC) and actinic keratosis in a 5% cream (Aldara) formulation85 but during treatment permanent postinflammatory hypo-pigmentation has been reported as a side-effect.86 Imiquimod is an immune response modifier and acts on the immune system by stimulating monocytes/macrophages and plasmacytoid dendritic cells in the epidermis and dermis to produce interferon-α and other immunostimulatory cytokines that stimulate cell-mediated immunity87 such as macrophages and the release of oxygen-reactive intermediates and other toxic molecules, finally leading to apoptosis of tumour cells.88 Topical imiquimod has been found to be effective for clearing superficial BCC in 85% of cases when used 3–5 times weekly for 6 weeks,89 and many studies have demonstrated that this regimen provides 88% histological clearance rate.90,91 Therefore, prolonged use of imiquimod may lead to increased occurrences of localized depigmentation.92

Imiquimod stimulates CD8 cells to become cytotoxic and induces maturation of Langerhans cells leading to enhancement of antigen presentation.93 Similarly, vitiligo may be mediated through antigen presentation by activated Langerhans cells with resultant destruction of melanocytes by cytotoxic T lymphocytes directed to melanocytes surface antigens,94 thus, causing depigmentation.

Imiquimod binds to Toll-like receptors (TLR) 7 and 8, which are cell-surface receptors. TLR7 activates a signalling cascade involving the myeloid differentiation factor 88-dependent pathway, upregulation of nuclear factor-κB and protein kinases. These signals evoke the T-helper (Th1) response and increase production of pro-inflammatory cytokines, mainly IFN-α, TNF-α and IL-12, all of which play a role in the pathogenesis of vitiligo. In addition, imiquimod promotes secretion of IL-6, IL-8 and IL-10, which are pro-inflammatory and pro-apoptosis cytokines that can cause vitiligo.95 Imiquimod augments the type 1 helper T-cell (TH1) response via the stimulation of these cytokines, which is found to be prominent in both the antitumour pathways and the pathogenesis of vitiligo.96-98 In promoting the regression and clearance of BCC, imiquimod can also induce changes that enhance the propensity towards apoptotic mechanisms by decreasing Bcl-2 expression, stimulating inflammatory infiltrate to the surrounding area and increasing expression of FasR on BCC cells.99,100

However, it is known that Bcl-2 is an antiapoptotic protein that protects cell viability without promoting proliferation. In normal epidermis, Bcl-2 expression is confined to the basal cell compartment and may serve to protect these cells from apoptosis.101 On the contrary, Bcl-2 protein expression and the apoptotic index were gradually modified during the course of the treatment with imiquimod because of many factors: a decrease of the antiapoptotic factors (Bcl-2) and/or an increase in the proapoptotic stimulus [cytotoxic T lymphocytes, natural cytotoxic T cells/killer cells, granzymes B, Fas, tumour necrosis factor (TNF), Bax, etc.].102 Schon et al. also reported that imiquimod induced apoptosis in squamous cell carcinoma cell lines and HaCaT cells because of the activation of several caspases and Bcl-2-dependent cytosolic translocation of cytochrome c from the mitochondria into the cytoplasm and subsequent cell death.103 Therefore, BCC cells become more susceptible to apoptosis through decreased Bcl-2 expression after imiquimod treatment.102

In a recent study, Kim et al. also reported about development of vitiligo-like hypo-pigmentary lesions after topical application of imiquimod because of the activation of caspase-3, Bcl-2 and mitogen-activated protein kinase expression in melanocytes, i.e., initiation of apoptotic activity.104 Therefore, these results might indicate that imiquimod can induce apoptosis of melanocytes, which will result in the loss of pigment cells.104 Thus, imiquimod represents a potential depigmenting agent (Tables 1 and 2).

**Side-effects**
The most common side-effects of imiquimod (Table 3) are burning, itching, pain at the target site, local skin reactions (i.e. erythema, erosion and scabbing/crusting)105 and hypo-pigmentation, which occur more frequently with twice-daily application.86

**Diphencyprone**
Diphencyprone or diphenylcyclopropenone (DPCP) is used to treat dermatological conditions resulting from an altered immunological state, such as extensive alopecia areata (AA). AA has been treated with DPCP since 1976 without serious adverse
events, except for the induction of hypo- or depigmentation. DPCP-induced vitiligo is rare and may represent a Koebner phenomenon in predisposed individuals. The initial depigmented patch usually arises at the site of DPCP application. Electron microscopic studies have confirmed that the depigmentation is not postinflammatory, evidence which supports the isomorphic phenomenon. It has been reported that patients can develop vitiligo even with DPCP concentrations as low as 0.0001%.

### Side-effects
Adverse effects include (Table 3) local eczema with blistering, regional lymphadenopathy, hyper-pigmentation, hypo-pigmentation and vitiligo.

As above explained, all three drugs are either toxic and/or expensive. Eligibility criteria for these drugs are not clear. Therefore, we suggest further research to investigate topical formulation of these agents as possible depigmenting therapies.

### Potential agents for depigmentation used for animal branding
Denton et al. identified compounds that had depigmenting properties for branding cattle. Subsequently, several depigmenting compounds have been experimentally discovered and tested in laboratory animals for branding purposes, without painful side-effects during or after application. In one study, eight compounds were selected on the basis of their known depigmenting effects, including: hydroquinone (H), 4-ethoxyphenol (4-EP),

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### Table 2: Comparison of established agents for depigmentation of normal skin in vitiligo universalis

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Mechanism of action</th>
<th>Dose/concentration</th>
<th>Onset of depigmentation</th>
<th>Side-effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MBEH</td>
<td>MBEH enzymatically converts to quinone, which reacts with proteins and DNA of melanocytes to induce melanocyte death</td>
<td>20% cream once to twice daily</td>
<td>1 month</td>
<td>Dermatitis, pruritus, xerosis, conjunctival melanosis and distal depigmentation</td>
<td>Mosher et al., Grojean et al.</td>
</tr>
<tr>
<td>2</td>
<td>Tretinoin with MBEH</td>
<td>Promoting the rapid loss of pigment through epidermopoesis, tyrosinase transcription and glycosylation</td>
<td>0.025–0.1%</td>
<td>10 days</td>
<td>Erythema, desquamation, dermatitis and distressing hyperpigmentation</td>
<td>Kasraee et al., Njoo et al.</td>
</tr>
<tr>
<td>3</td>
<td>4-methoxyphenol</td>
<td>Tyrosinase inhibition</td>
<td>20% cream</td>
<td>4–12 months</td>
<td>Skin irritation but less than MBEH</td>
<td>Njoo et al.</td>
</tr>
<tr>
<td>4</td>
<td>Laser</td>
<td>Selectively targeting melanocytes for destruction by photothermolysis</td>
<td>Different wavelengths of Q-switched lasers like 1064, 755, 694 and 532 nm</td>
<td>Might require multiple sessions</td>
<td>Painful; requires local anaesthesia</td>
<td>Njoo et al.</td>
</tr>
<tr>
<td>5</td>
<td>Cryotherapy</td>
<td>Melanotoxic</td>
<td>Liquid nitrogen for 10–20 s</td>
<td>4 weeks</td>
<td>Permanent scarring, if performed aggressively</td>
<td>Radmanesh</td>
</tr>
<tr>
<td>6</td>
<td>Cryotherapy and 4-hydroxyanisole</td>
<td>Melanotoxic</td>
<td>20% cream of 4-hydroxyanisole</td>
<td>3 weeks</td>
<td>Skin irritation</td>
<td>Nuzzo and Massotti</td>
</tr>
</tbody>
</table>

MBEH, monobenzyl ether of hydroquinone.

### Table 3: Comparison of potential depigmenting agents for depigmenting the normal skin in vitiligo universalis

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Mechanism of action</th>
<th>Dose/concentration</th>
<th>Onset of depigmentation</th>
<th>Side-effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Imatinib</td>
<td>Tyrosine kinase inhibitor</td>
<td>800 mg/day for 6 months by the systemic route</td>
<td>4 weeks</td>
<td>Periorbital oedema, fluid retention, nausea, emesis, diarrhoea and myelosuppression</td>
<td>Tsao et al.</td>
</tr>
<tr>
<td>2</td>
<td>Imiquimod</td>
<td>Stimulation of the innate immune response and cell-mediated adaptive immunity</td>
<td>5% cream</td>
<td>3 months</td>
<td>Burning, itching and pain at the target site</td>
<td>Senel and Seckin, Sripakash and Godbolt</td>
</tr>
<tr>
<td>3</td>
<td>Diphencyprone</td>
<td>Immunomodulatory action</td>
<td>0.0001%</td>
<td>10.5 months</td>
<td>Local eczema with blistering, regional lymphadenopathy and contact urticaria</td>
<td>Pan et al.</td>
</tr>
</tbody>
</table>
4-methylcatechol (4-MC), 4-tert-butylcatechol (4-t-BC), 4-methoxyphenol (4-MP), monobenzone (M), hydroquinone bis (2-hydroxyethyl)-ether (HHEE) and catechol (C). These compounds were injected into animal skin as 10% and 20% solutions dissolved in 95% ethanol. Six of the eight compounds tested showed positive depigmenting effects at 10% except C and HHEE.111 These results also revealed that compounds screened at concentrations of 10% were superior to those injected at 20% because of their ability to produce a depigmenting effect with minimal necrosis.111

Both 4-MC and 4-MP were also applied topically in a cream (liposome) base onto the same animal previously used to screen eight compounds at 10% according to the technique that has been previously described by Bangham et al. for incorporating these compounds into a liposome base.112 This liposome preparation was applied in a rub-in form on the same animal after it had been clipped and swabbed as described previously. A stencil held tightly against the skin was used as a guide in which 0.5 mL of the preparation was rubbed into the skin with a cotton swab until all the material had been absorbed. The cream base was applied alone in the same manner beneath the treatment site to serve as a control. At the end of the experiment, it was observed that there was no visible depigmentation of the epidermis as result of topical application of compounds, possibly because an inadequate amount of compounds was absorbed into the skin. Shafer-Korting et al. also explained about the lack of penetration of drugs into the skin due to failure of the drug to penetrate the horny layer of the skin and low absorption rates due to drugs remaining in the liposomes.113

Certain of these compounds should be further investigated as topical depigmenting agents for use in humans with vitiligo universalis (Table 1).

**Side-effects**

Inflammation was observed at both 10% and 20% concentrations for the 4-MC, 4-MP and M. Substantial dermal necrosis was observed at all sites where compounds had been injected at a concentration of 20%.111

**Conclusions**

Vitiligo is a common depigmenting disorder. Vitiligo universalis patients wish to be depigmented rather than attempt repigmentation therapy if vitiligo covers more than half of their bodies. There are many depigmenting therapies and agents (Table 1) described in the literature for depigmenting the skin to obtain a more fair colour for cosmetic purposes. However, very few therapies or agents are available to depigment the pigmented skin to achieve uniform skin colour in patients with vitiligo universalis. To the best of our knowledge, there is no such review about depigmenting agents for vitiligo universalis that compares the advantages and disadvantages of the available agents. In this review, we compared advantages, mechanisms of action, concentration, costs and disadvantages of available depigmenting agents (Table 2). In this review, we also proposed few potential depigmentation agents for further research (Table 3) such as Imatinib, Imiquimod and Diphencyprone. These agents were used for curing some other diseases but as side-effects they caused depigmentation on the skin. We propose that these agents and some depigmentation agents used for branding cattle to be investigated as topical potential depigmenting agents. In addition, this review has revealed that MBEH is the most safe and effective depigmenting agent.

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