

# Photosensitisation diseases of animals: Classification and a weight of evidence approach to primary causes



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## ABSTRACT

Clare's (1952) classification system for photosensitisation diseases (types I, II, III and Uncertain) has endured many years of use despite some confusion regarding his secondary, or type III, category, as well as the more recent discovery of two mechanisms (types I and II) of phototoxicity. Therefore, to reduce confusion in terminology, I propose that Clare's four groups be known as *primary* (or direct), *secondary* (indirect or hepatogenous), *endogenous* (aberrant porphyrin synthesis), and *idiopathic*. The use of the word *type* can then be reserved for the mechanisms of phototoxicity. Clare's (1952, 1955) papers listed three plants as primary photosensitisers and three as idiopathic. In the literature, several other plants have been associated with photosensitisation in farm animals. Most of these are likely to have a primary pathogenesis; however, the weight of evidence for all but a few is sparse. With respect to plants (and certain mycotoxins and insects) implicated in primary photosensitisation outbreaks, McKenzie's "toxicity confidence rankings" (*Australia's Poisonous Plants, Fungi and Cyanobacteria*, 2012) has been adapted to "phototoxic agent confidence rankings". Thus, plants, mycotoxins or insects can be categorised regarding phototoxicity, i.e. definite (A); some evidence (B); suspected (C); or phototoxin isolated but no field cases known (D), and weight of evidence, i.e. field cases (1); experimental feeding produces photosensitisation (2); phototoxin isolated (3); phototoxin produces photosensitisation experimentally (4); and/or correlation of the action spectrum/chromatogram in blood or skin with the absorption spectrum/chromatogram of the phototoxin (5). As a result, confidence rankings ranging from A5 to D1 can be allocated. From the available literature, at least seventeen plant species can be ranked as A5 (definite phototoxicity with a maximum weight of evidence). The relatively recent breakthrough regarding the discovery of phototoxic anthraquinones in *Heterophyllaea* spp. has led to the serendipitous association of the same and similar anthraquinones as the most likely phototoxins in alligator weed (*Alternanthera philoxeroides*).

## 1. Introduction

*Photosensitisation* is a noncontagious clinical syndrome that develops when an animal or human becomes abnormally reactive to sunlight due to the presence of a *phototoxin* or *photoallergen* in or on the skin (Clare, 1952; Epstein, 1999). The signs are characterised by cutaneous hyperaesthesia and varying degrees of dermatitis and/or keratoconjunctivitis, and occur in skin and/or eye membranes that are unprotected by melanin pigmentation, thickness of the epidermis, or coverage by hair, wool or clothing (Clare, 1952; Seawright, 1982; Epstein, 1999).

In farm animals, most cases of photosensitisation are due to *phototoxicity* where the phototoxin is an exogenous or endogenous photo-reactive compound located within capillaries or dermal soft tissues of the exposed skin, exposed mucous membranes or eyes. In almost all cases, the phototoxin, the identity of which may be known or unknown, is contained within pasture plants, forages or weeds. Certain plant phototoxins, but not all, can exert their effects following skin contact

and light exposure (called phytophoto-contact dermatitis), as well as following ingestion. A phenomenon of vital importance in human pharmacology and cosmetic development is that some drugs have a side-effect of phototoxicity.

Phototoxins become toxic when exposed to light. They are compounds that have fluorescent properties and resonating, often tricyclic structures and aromatic rings, and absorb light wavelengths within the ultraviolet (UV) and visible spectrum (~280–700 nm) (Harber and Baer, 1972). Most phototoxins are pigments because only a substance that absorbs light can be sensitised by light (Clare, 1952).

Phototoxicity is a quantum chemical phenomenon. An absorbed light photon promotes electrons within the phototoxin molecule from a stable ground to an excited state, known as a singlet or triplet state. These are higher energy states defined by the spin state of the two highest energy electrons. When the two electrons have opposite spins, the electronic state is singlet; when they have the same spin, it is triplet. The short-lived excited singlet state is rapidly converted to the

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corresponding triplet state by intersystem crossing. In the presence of molecular oxygen ( $O_2$ ), two competing reactions of the long-lived triplet state of the phototoxin can occur to produce reactive oxygen species. The triplet state phototoxin may react with other molecules to transfer a hydrogen atom or electron so that it becomes a radical itself that then reacts with  $O_2$  to yield radicals or radical ions (e.g. superoxide anion and hydroxyl radical) (type I phototoxicity mechanism). Alternatively, it may transfer energy directly to  $O_2$  to form the electronically excited singlet molecular oxygen ( $^1O_2$ ) (type II mechanism) (Foote, 1991; Núñez Montoya et al., 2005). The singlet oxygen generating abilities of known phototoxins vary according to their quantum yield (DeRosa and Crutchley, 2002; Núñez Montoya et al., 2005; Redmond and Gamlin, 1999). In a type II phototoxicity reaction, it has been estimated that each molecule of phototoxin can produce  $10^3$ – $10^5$  molecules of singlet oxygen before being degraded (DeRosa and Crutchley, 2002). Susceptible substrates within cells (e.g. lysosomes, mitochondria, cell membranes, lipids, proteins, nucleic acids) then undergo a destructive cascade of chain reactions resulting in the clinical signs and characteristic lesions of photosensitisation (Seawright, 1982).

Not all fluorescent compounds are effective photosensitisers. For a compound to be an effective phototoxin in animal tissues, it should: (1) be absorbed from the gastrointestinal tract or through the skin in sufficient concentration; (2) be readily transformed to an excited state by a photon of light of appropriate wavelength; (3) be able to be electronically excited and possess sufficient energy to trigger a type I and/or type II phototoxic reaction to generate reactive oxygen species; (4) have an excited state with a high enough quantum yield and adequate lifetime; and (5) be stable enough to enable the reaction to take place (DeRosa and Crutchley, 2002).

Another less common form of photosensitisation involves some sort of photoallergen. In humans, *photoallergy* is an uncommon, acquired, immune-mediated, immediate (e.g. solar urticaria) or delayed-type hypersensitivity reaction that is similar to contact allergy and that occurs 24–48 h after exposure to a photoallergen (usually a chemical, or drug) in the presence of UV light (Epstein, 1999). Possible examples of photoallergic dermatitis in farm animals include reactions to gluten (Yeruham et al., 1999) and cocoa shells (Yeruham and Avidar, 2003) in the diets of horses and cattle, respectively.

*Sunburn* is a normal reaction of unprotected skin to sunlight, particularly wavelengths in the UV-B (280–315 nm) spectrum which window glass blocks (Clare, 1952). Sunburn does not require the presence of oxygen. It is commonly seen especially on the faces of horses that have unpigmented skin (Seawright, 1982), as well as in white pigs, goats and cows (Mauldin and Peters-Kennedy, 2016).

The term *photodermatitis* is broader and includes photosensitisation and *photo-aggravated dermatitis* (increased sensitivity to UV radiation without the presence of a phototoxin) due to an underlying disease process such as dermatomyositis, discoid lupus erythematosus, pemphigus erythematosus, and erythema multiforme (Kutlubay et al., 2014).

*Phytophoto-contact dermatitis* is caused by nonallergic contact with certain plants particularly from the plant families Apiaceae, Rutaceae, Moraceae, and Fabaceae, that contain furanocoumarins (psoralens), in the presence of UV-A (315–400 nm). In this type of photosensitisation, which is more prevalent in humans (often referred to as *photo-irritation*) than in animals, burning and itching begin within 24 h and may progress to large blisters 48–72 h after exposure (Baker et al. 2017).

The syndrome of forage-associated photosensitisation in livestock is a sporadic condition worldwide, but in some countries it can be of major economic and animal welfare importance. In New Zealand, for example, thousands of sheep and cattle are affected by clinical or subclinical facial eczema (sporidesmin toxicosis), a secondary (hepatogenous) photosensitisation, each year. Furthermore, sporadic outbreaks of idiopathic photosensitisation, such as spring eczema in calves and dairy cows, which occurs countrywide during spring, and in lambs on unimproved pastures in the South Island, have frustrated farmers and veterinarians for many years. The evidence so far indicates that most of these cases are primary,

i.e. associated with some sort of ingested phototoxic plant. When veterinarians are called to investigate such cases and advise on treatment and prevention, two issues frequently come to the fore. One, what is the cause (in some cases the “evidence” may have already been eaten), and two, what is the mechanism or pathogenesis, i.e. is it secondary to liver injury, or is it due to an endogenous or exogenous phototoxin?

Over the years, many plants and feed types, including certain valuable forages that are normally considered innocuous, have been associated with photosensitisation. For most of these, the actual evidence regarding the pathogenesis, nature of the phototoxin, and the presence or absence of hepatotoxicity, is vague, anecdotal or fragmentary. Sometimes, a diagnosis is made “by exclusion”. Even when photosensitisation is experimentally reproduced through feeding or dosing, the phototoxin often remains undiscovered. Furthermore, outbreaks may be transient and associated with certain times of the year, weather conditions or growth stage or disease status of the offending plants. Even when the offending plant is known with almost complete certainty, the ongoing difficulties in reproducing photosensitisation can be extremely frustrating. This is compounded by the stringent but understandable requirements of modern institutional animal ethics committees. For these reasons, continued surveillance and reporting of observations and objective data are necessary (Casteel et al., 1991; Smith, 1987).

In this paper, in an attempt to reduce confusion, I propose a refinement of Clare’s classification of photosensitisation diseases (Clare, 1952). I also propose a new weight of evidence approach for categorising primary photosensitisations in farm livestock. Although I have attempted to consult all of the available literature up until 2018, there will be (no doubt) omissions or other inadequacies.

## 2. Clare’s classification of photosensitisation diseases

The four-category classification of photosensitisation diseases (Clare, 1952), namely, type I (primary), type II (aberrant endogenous pigment synthesis), type III (hepatogenous), and Uncertain aetiology, is logical and has endured for many years. However, confusion arises since type III, is also often referred to as “secondary” to liver damage, implying that a more appropriate designation would be type II.

## 3. Mechanisms of phototoxicity

A further point of confusion is that which has arisen with the classification of *in vitro* oxygen-dependent phototoxicity reactions, referred to above, as type I (electron transfer generating radicals or radical ions such as the superoxide anion) or type II (energy transfer generating the non-radical but highly toxic singlet oxygen) (DeRosa and Crutchley, 2002; Foote, 1991). In a review in Photochemistry and Photobiology in 2017, the authors stated: “We believe that communication among photoscientists is less than optimal and unintentionally vague. Overcoming this language barrier is crucial for more consistent and precise mechanistic interpretations of photosensitized oxidation reactions. It should be mentioned that type III and type IV photosensitization reactions that only applied to oxygen-independent photoreactions have also been proposed in the literature” (Baptista et al., 2017). Of relevance here is that the phototoxicity of the furanocoumarins, important constituents of a number of plants ingested or contacted by animals and humans, involves types I and II as well as the oxygen-independent type III (photobinding) reactions (Llano et al., 2003).

## 4. Proposed unambiguous classification of photosensitisation diseases

In the light of the above, it seems logical to revise Clare’s four categories of the pathogenesis of photosensitisation as primary (or direct), secondary (indirect or hepatogenous, with phytoporphyrin the phototoxin), endogenous (aberrant porphyrin synthesis) (Smith and O’Hara, 1978), and idiopathic (cause and/or mechanism unknown) (Table 1).

**Table 1**

Unambiguous classification of the photosensitisation diseases of animals referred to by [Clare \(1952, 1955\)](#).

Pathogenesis	Plant/mycotoxin/drug/disease	Phototoxin
Primary (direct)	<i>Hypericum perforatum</i>	Hypericin
	<i>Fagopyrum esculentum</i>	Fagopyrin
	<i>Ammi visnaga</i>	Furanocoumarins
	Phenothiazine	Phenothiazine sulphoxide
	Chlorophyll derivatives	Pheophorbide a and other chlorins
Secondary (indirect)	<i>Tribulus terrestris</i>	Phytoporphyrin (= phylloerythrin)
	Facial eczema	
	<i>Panicum</i> spp.	
	<i>Nolina texana</i>	
	<i>Agave lechuguilla</i>	
	<i>Holocalyx balansae</i>	
	<i>Myoporium laetum</i>	
	<i>Brachiaria brizantha</i>	
	<i>Narthecium ossifragum</i>	
	<i>Lippia</i> spp.	
	<i>Lantana camara</i>	
	<i>Verbena officinalis</i>	
	<i>Kochia scoparia</i>	
	<i>Tetradymia</i> spp.	
	Mouldy <i>Cynodon dactylon</i> grass	
	Cyanobacteria	
	Congenital Southdown photosensitivity	
	Rift Valley fever	
	Lupinosis	
	Copper poisoning	
	Carbon tetrachloride poisoning	
	Phosphorus poisoning	
Bovine erythropoietic porphyria	Uro- and coproporphyrins	
Endogenous (aberrant haem pigment synthesis)		
Idiopathic	<i>Trefoil dermatitis</i> <sup>a</sup>	Unknown
	<i>Brassica napus</i> (rape)	
	<i>Erodium</i> spp.	

<sup>a</sup> Also called clover disease or trifoliosis, associated with *Trifolium* and *Medicago* spp.

## 5. Blum's postulates revisited

As emphasised by [Clare \(1952\)](#), certain facts need to be established in an investigation of a photosensitisation disease. These requirements were summarised as three postulates ([Blum, 1941](#)), as follows: (1) signs of photosensitisation are elicited by exposure to sunlight preferably through window glass (to distinguish the condition from sunburn); (2) a photodynamic substance (phototoxin) must be isolated in pure form, and produce the same clinical signs following injection (or dosing) in experimental animals exposed to sunlight; and (3) the wavelengths that produce sensitivity in postulates 1 and 2 are identical. When Blum published his work, he was satisfied that hypericium (St. John's wort poisoning) satisfied the first and second postulates but not the third, while fagopyrism (buckwheat poisoning) satisfied the first only, and clover disease (trefoil dermatitis) none ([Blum, 1941](#)).

## 6. Absorption and action spectra: Blum's additional postulates

Furthermore, the absorption spectrum of a purified phototoxin should show a remarkable similarity to the action spectrum (magnitude of the photobiological response in a photosensitised animal's tissues plotted against wavelength of radiation) ([Blum, 1941](#)). Accordingly, [Blum \(1941\)](#) proposed four more postulates, summarised as follows: (1) the limits of an action spectrum probably correspond to the limits of an absorption band of the phototoxin; (2) strong similarities between the absorption and action spectra should be anticipated; (3) if they do not

agree completely, a maximum of the action spectrum is not to be expected in the region of the minimum absorption; and (4) two or more photobiological processes having similar action spectra may have the same substance or similar substances as their light absorbers.

## 7. Plants associated with primary photosensitisation

[Clare \(1952\)](#) believed that many plants with an uncertain photosensitising pathogenesis were probably primary, and said, "some of these have been known for many years but are so sporadic and transient in their occurrence that they offer little opportunity for experimental studies, although the accumulating field evidence may indicate that a particular plant ... is responsible."

Since [Blum \(1941\)](#) and [Clare \(1952, 1955\)](#), more plants have been added to the list of primary photosensitisers on the basis of the absence of liver damage, as shown by liver enzyme activities in blood being within the normal reference ranges, or no abnormalities on gross or histological examination of the liver in photosensitised animals. In many of these, however, the responsible phototoxin has not been identified. Nor have phytoporphyrin (= phylloerythrin) concentrations been measured in the blood of affected animals ([Campbell et al., 2010](#)) in order to rule out a functional disturbance of the liver that could lead to a derangement in the normal phytoporphyrin excretion, such as occurs in congenital Southdown photosensitisation ([Clare, 1952](#)). In affected Southdown sheep, secondary photosensitisation with marked phytoporphyrinaemia occurs in the absence of gross or biochemical liver injury ([Clare, 1955](#)).

By the year 2000, the only "new" phototoxins of plant origin that had been added to hypericin and fagopyrin was the chemical identification of furanocoumarins in such primary photosensitising plants as *Ammi majus*, *Cymopterus watsonii*, *Pastinaca sativa* (cultivated and wild parsnip), *Apium graveolens* (celery) (all Apiaceae) and *Thamnosma* spp. (Rutaceae) ([Murray et al., 1982](#)).

## 8. Photosensitising anthraquinones in *Heterophyllaea pustulata* (Rubiaceae)

What I believe to be a remarkable breakthrough came about when a group of research workers, searching for new antimicrobial compounds in indigenous flora in Argentina, elected to study *Heterophyllaea pustulata* Hook. f., a shrub known locally as "cegadera". Cegadera grows at high altitudes in the Andes Mountains in northwest Argentina and Bolivia ([Núñez Montoya et al., 2003](#)). Natural intoxication by cegadera, characterised by typical lesions of photosensitisation dermatitis of non-pigmented and sparsely coated skin, as well as corneal oedema, keratitis, and progressive blindness in severe cases without elevation of liver enzyme activities, has been reported in cattle, sheep, goats and horses ([Aguirre and Neumann, 2001](#); [Hansen and Martiarena, 1967](#); [Micheloud et al., 2017](#)). Experimentally, ingestion of dried leaves, flowers and fruit of cegadera caused typical signs of photosensitisation in guinea pigs, rabbits, sheep and cattle; the photosensitising substances, however, were not investigated at the time ([Hansen and Martiarena, 1967](#)).

The Argentinian research workers took various solvent extracts of air-dried cegadera leaves and stems and subjected them to phytochemical investigations ([Harborne, 1984](#)). Benzene extracts examined by Silica gel chromatography yielded fractions from which the "free" (aglycone) anthraquinones soranjidiol, rubiadin, soranjidiol-1-methyl ether, rubiadin-1-methyl ether, damnacanthal, damnacanthol, heterophylline and pustuline, as well as the bianthraquinone, 5,5'-bisoranjidiol, were obtained ([Núñez Montoya et al., 2006](#); [Núñez Montoya et al., 2003](#)). The fact that extracts were so rich in aglycone anthraquinones, some of which were known to possess antimicrobial activities, led to further investigations. Most of these anthraquinones were shown to have photosensitising properties *in vitro* through the generation of superoxide anion (O<sub>2</sub><sup>-</sup>) (type I mechanism) as well as singlet

**Table 2** Weight of evidence confidence rankings for phototoxic plants and other agents (adapted from McKenzie, 2012).

Weight of evidence	Field evidence	Consistent for several incidents *	Experimental feeding to at least one animal species produces photosensitisation	Yes * or Not attempted	Phototoxin isolated and/or type I or type II phototoxicity demonstrated <i>in vitro</i>	Yes * or No	Phototoxin isolated experimentally reproduces photosensitisation	Yes * or Not attempted	Correlation of action spectrum/ chromatogram in serum or skin with the absorption spectrum/ chromatogram of the pure phototoxin	Yes * or Not attempted	Rank (no. of *) range
A Definite phototoxicity				Yes * or Not attempted		Yes * or No		Yes * or Not attempted		Yes * or Not attempted	A1-5
B Some evidence of phototoxicity		Consistent for several incidents or a well-documented single case * or no reports		Yes * or Not attempted		Yes * or No		-		-	B1-3
C Suspected of phototoxicity		Poor or inconsistent		Yes * or Not attempted		Yes * or No		-		-	C1-2
D Phototoxin isolated, but no field cases known		No reports		Not attempted		Yes *		-		-	D1-2

oxygen ( $^1O_2$ ) (type II mechanism) (Comini et al., 2007; Núñez Montoya et al., 2005). Soranjidiol and rubiadin were the two anthraquinones found in the highest concentrations in the aerial parts of cegadera (Núñez Montoya et al., 2003) and they also generated the highest yields of  $^1O_2$  and/or  $O_2^-$  when irradiated (Núñez Montoya et al., 2005). In controlled *in vivo* experiments, extracts of cegadera that contained soranjidiol and rubiadin as the predominant anthraquinones were administered to mice via oral or subcutaneous routes and typical signs of photosensitisation were induced following exposure to 160 min of sunlight. The mice were then sacrificed and serum and skin samples were processed with solvents and subjected to HPLC analysis. Chromatograms obtained from the serum and skin of the mice showed remarkable correlation with those of soranjidiol and rubiadin in the original cegadera extracts (Núñez Montoya et al., 2008).

The only other species in the *Heterophyllaea* genus, *H. lycioides* (Rusby) Sandwith, found in mountainous regions of Bolivia and Peru, has also been examined for photosensitizing anthraquinones (Dimmer et al., 2017). Seven aglycone anthraquinones, including four (soranjidiol, heterophylline, pustuline and 5,5'-bisoranjidiol) previously found in *H. pustulata*, were obtained. The three new anthraquinones were lycionine, 5-chlorosoranjidiol and 7-chlorobisoranjidiol (Dimmer et al., 2017).

The systematic process by which the researchers in Argentina went about finding the cegadera phototoxins deserves special attention. They:

- first identified the plant species that was associated with definite phototoxicity (Hansen and Martiarena, 1967; Núñez Montoya et al., 2003); then they
- subjected extracts of plant material to intensive chemical investigation targeted towards pigments and fluorescent compounds (Núñez Montoya et al., 2006; Núñez Montoya et al., 2003); then they
- investigated type I and type II photosensitizing properties in promising plant extracts *in vitro* (Comini et al., 2007; Núñez Montoya et al., 2005); then
- carried out controlled *in vivo* experiments with promising plant extracts or isolated compounds (Núñez Montoya et al., 2008); and finally they
- analysed serum and/or skin from experimentally photosensitised animals to confirm a match between the action spectrum/chromatogram with the absorption spectrum/chromatogram of the incriminated phototoxin(s) (Núñez Montoya et al., 2008).

This process enabled them to confirm that certain aglycone anthraquinones are phototoxic and thereby add them to the list of plant compounds associated with definite primary phototoxicity.

## 9. Phototoxic plant (or other agent) weight of evidence confidence rankings

I believe that the approach followed by the cegadera investigators should be regarded as the “gold standard”. But, how does the weight of evidence of other primary or idiopathic photosensitisations compare? A classification system for poisonous plant toxicity confidence rankings based on the “weight of evidence” has been published (McKenzie, 2012). I have adapted this classification system to one for phototoxic plants and other agents, as shown in Table 2. Based on this classification, the weight of evidence confidence rankings for plants or other agents as causes of primary photosensitisation are provided in Tables 3–9.

## 10. Classes of phototoxin known to date

As can be seen from Tables 3, 6, 8 and 9, there are only four main classes of phototoxin (with the exception of the perloine alkaloid) incriminated in phototoxic photosensitisations in farm animals. They are perylenequinones, aglycone anthraquinones, furanocoumarins, and derivatives of chlorophyll (pheophorbide a and phytoporphyrin). The respective structures are shown in Fig. 1.



**Table 3**  
Primary photosensitising plants that show definite phototoxicity with a maximum weight of evidence (A5).

Plant	Plant family	Phototoxin(s)	Citations
<i>Heterophyllaea<sup>a</sup> pustulata</i> Hook. f. (cegada)	Rubiaceae	Anthraquinones - soranjidiol, rubiadin, damnacanthal and others	(Comini et al., 2007; Micheloud et al., 2017; Núñez Montoya et al., 2008; Núñez Montoya et al., 2003; Núñez Montoya et al., 2005)
<i>Hypericum<sup>b</sup> perforatum</i> L. (St. John's wort)	Hypericaceae	Perylenequinone – hypericin <sup>c</sup>	(Araya and Ford, 1981; Blum, 1941; Bourke, 2000, 2003; Bourke and White, 2004; Cunningham, 1947; Diwu and Lown, 1993; Gattuso et al., 2017; Henry, 1922; Kingsbury, 1964; Pace, 1942; Southwell and Bourke, 2001; Southwell and Campbell, 1991)
<i>Hypericum triquetrifolium</i> Turra (= <i>H. crispum</i> )	Hypericaceae	Perylenequinone - hypericin	(Bale, 1978; Blum, 1941; Kitanov, 2001)
<i>Hypericum maculatum</i> Crantz	Hypericaceae	Perylenequinone - hypericin	(Blum, 1941; Kitanov, 2001)
<i>Fagopyrum esculentum</i> Moench (buckwheat)	Polygonaceae	Perylenequinone – fagopyrin <sup>d</sup>	(Blum, 1941; Kingsbury, 1964; Sheard et al., 1928; Wender, 1946)
<i>F. tartaricum</i> (L.) Gaertn.	Polygonaceae	Perylenequinone - fagopyrin Linear furanocoumarins:	Eguchi et al. (2009)
<i>Ammi majus</i> L. (Bishop's weed)	Apiaceae	Xanthotoxin, bergapten, ammirin, imperatorin, alloimperatorin, marmesin, marmesinin, oxypeucedanin	(Dall'Acqua, 1988; Ivie, 1978; Llano et al., 2003)
<i>A. visnaga</i> (L.) Lam.	Apiaceae	Xanthotoxin, 8-hydroxybergapten, imperatorin, marmesin	(Dollahite et al., 1978; Eyged et al., 1974; Kellerman et al., 2005; Méndez et al., 1991; Murray et al., 1982; Schild et al., 2004; Witzel et al., 1978)
<i>Cymopterus watsonii</i> (Coul. & Rose) Jones (spring parsley)	Apiaceae	Xanthotoxin, bergapten	(Le Quesne et al., 1985; Murray et al., 1982; Shlosberg et al., 1974)
<i>Pastinaca sativa</i> L. (wild parsnip)	Apiaceae	Xanthotoxin, bergapten, imperatorin, isopimpinellin	(Binns et al., 1964; Murray et al., 1982)
<i>Apium graveolens</i> L. (celery) infected by <i>Sclerotinia sclerotiorum</i> (Lib.) de Bary ("pink rot")	Apiaceae	Xanthotoxin, 4,5',8-trimethylpsoralen, bergapten, 8-hydroxybergapten, isopimpinellin, isoimperatorin, rutaretin	(Montgomery et al., 1987a, 1987b; Murray et al., 1982; Stegelmeier et al., 2015)
<i>Bituminaria bituminosa</i> (L.) C.H. Stirt.	Fabaceae	Psoralen	(Montgomery et al., 1987a, 1987b; Murray et al., 1982; Perone et al., 1964; Scheel et al., 1963)
<i>Cullen</i> spp.	Fabaceae	Psoralen	(Del Rio et al., 2010; Innocenti et al., 1997; Murray et al., 1982)
<i>Ruta graveolens</i> L. (rue)	Rutaceae	Psoralen, bergapten, isopimpinellin, isoimperatorin, chalepensis, marmesin, isorutarin	(Del Rio et al. (2010)
<i>Thamnosma texana</i> (Gray) Torr. (Dutchman's breeches)	Rutaceae	Psoralen, xanthotoxin, bergapten, isopimpinellin	(Gault et al., 2015; Murray et al., 1982)
<i>T. montana</i> Torr. & Frem.	Rutaceae	Psoralen, xanthotoxin, bergapten, isopimpinellin, isoimperatorin	(Oertli et al., 1983, 1984)
<i>Zephyranthes drummondii</i> D. Don (syn. <i>Cooperia pedunculata</i> Herbert) (rain lily) dead leaves possibly infected with a fungus such as <i>Sclerotinia sclerotiorum</i> <sup>e</sup>	Amaryllidaceae	Not investigated, but likely to be furanocoumarins	(Kutney et al., 1972; Murray et al., 1982)

<sup>a</sup> Although experimental feeding has not been attempted, there is field evidence that the only other representative of the *Heterophyllaea* genus, *H. lycioides* (Rusby) Sandwith, which also contains anthraquinones, causes primary photosensitisation (Dimmer et al., 2017).

<sup>b</sup> Several other *Hypericum* spp., namely *H. aethiopicum* Thunb., *H. revolutum* Vahl (*H. leucoptychodes*), and *H. pulchrum* L. have been associated with field cases of photosensitisation and were confirmed experimentally (Blum, 1941; Cunningham, 1956; Kellerman et al., 2005; Quin, 1933). Since the phototoxin is likely to be a perylenequinone (i.e. hypericin), they can probably be added to this list. Note that not all *Hypericum* spp. are phototoxic. For example, animal testing with *H. androsaemum* L. (tutsan) has proved negative (Cunningham, 1947).

<sup>c</sup> Another perylenequinone, pseudohypericin, is frequently present in various hypericums at greater or lesser concentrations than hypericin (Kitanov, 2001; Vandenbergae et al., 1998).

<sup>d</sup> Several fagopyrin derivatives have been isolated from buckwheat (Benković et al., 2014).

<sup>e</sup> *Sclerotinia sclerotiorum* has a very broad host range including Poaceae (grasses), Araceae (arum family), and Liliaceae (lily family) of the Monocotyledoneae (Boland and Hall, 1994). Conceivably, this or a similar fungus could infect the Amaryllidaceae and induce the formation of furanocoumarin phytoalexins.

**Table 4**  
A2 primary photosensitising plants that show definite phototoxicity (field evidence and experimental feeding resulted in photosensitisation).

Plant	Plant family	Phototoxin(s)	Citations
<i>Froelichia humboldtiana</i> (Roem. Et Schult.) Seub.	Amaranthaceae	Unknown	(Knupp et al., 2014; Pimentel et al., 2007; Santos et al., 2017; Souza et al., 2012)
<i>Brassica napus</i> L. (Biennis group) (fodder rape) and <i>B. rapa</i> L. (leafy or bulb turnip)	Brassicaceae	Unknown	(Anonymous, 1947; Clare, 1955; Cunningham et al., 1942; Filmer, 1947)
<i>Chamaesyce (Euphorbia) maculata</i> (L.) Small	Euphorbiaceae	Unknown	Kingsbury (1964)
<i>Malachra fasciata</i> Jacq.	Malvaceae	Unknown	De Araújo et al. (2017)
<i>Biserrula pelecinus</i> L.	Fabaceae	Unknown	(Kessell et al., 2015; Quinn et al., 2018; Swinny et al., 2015)

## 11. Analytical phytochemistry techniques

Because of the risks of photosensitisation and photo-irritation posed by new drugs, topical agents and cosmetics for human use, a number of methods for *in vitro* testing for phototoxicity have been developed

(Spielmann et al., 1994). One of these, the simple *Candida albicans* yeast phototoxicity assay has proved useful to identify plants and fungus-infected plant tissues that contain furanocoumarins (Rowe and Norman, 1989). This test, however, does not detect anthraquinone- nor perylenequinone-containing plants. Methods of extraction and analysis of

**Table 5**

B2 plants that show some evidence of primary phototoxicity (field evidence and experimental feeding resulted in photosensitisation).

Plant	Plant family	Phototoxin(s)	Citations
<i>Medicago nigra</i> (L.) Krockner (syn. <i>M. denticulata</i> , <i>M. polymorpha</i> ) (bur medick, common trefoil)	Fabaceae	Unknown	(Bull and Macindoe, 1926; Byrne, 1937; Dodd, 1916; Hurst, 1942; McKenzie, 2012; O'Gorman, 1920)
<i>Erodium moschatum</i> (L.) L'Hér. and <i>E. cicutarium</i> (L.) L'Hér. (storksbill)	Geraniaceae	Unknown	(Anonymous, 1947; Connor, 1977; Filmer, 1947; Ford, 1965; Hurst, 1942; Stroebel, 2002)

**Table 6**

B2 plants that show some evidence of primary phototoxicity (field evidence and phototoxin(s) isolated).

Plant	Plant family	Phototoxin(s)	Citations
<i>Alternanthera philoxeroides</i> (Mart.) Griseb. (alligator weed)	Amaranthaceae	Anthraquinones – rubiadin, rubiadin 1-methyl ether and 2-hydroxy-3-methyl anthraquinone	(Anonymous, 1989; Bourke and Rayward, 2003; Fan et al., 2008)

**Table 7**

B1 plants that show some evidence of primary phototoxicity (field evidence only).

Plant	Plant family	Phototoxin(s)	Citations
<i>Medicago sativa</i> (lucerne, alfalfa)	Fabaceae	Unknown	(Byrne, 1937; House et al., 1996; Puschner et al., 2016)
<i>Trifolium repens</i> L. (white clover)	Fabaceae	Unknown	McKenzie (2012)
<i>Trifolium pratense</i> L. (red clover)	Fabaceae	Unknown	McKenzie (2012)
<i>Trifolium subterraneum</i>	Fabaceae	Unknown	Filmer (1929)
<i>Trifolium resupinatum</i> L. (Persian clover, shaftal)	Fabaceae	Unknown	(McKenzie, 2012); Government agency and seed merchant factsheets
<i>Trifolium hybridum</i> (Alsike clover)	Fabaceae	Unknown	(Fincher and Fuller, 1942; Nation, 1989; Stegelmeier, 2002)
<i>Lotus corniculatus</i> L. (birdsfoot trefoil)	Fabaceae	Unknown	Stafford et al. (1995)
<i>Echinochloa frumentacea</i> Link (barnyard grass, Japanese millet <sup>a</sup> )	Poaceae	Unknown <sup>b</sup>	(Allen et al., 2004; Anonymous, 1947; Hart, 1966)

<sup>a</sup> *Echinochloa esculenta* (A. Braun) H. Scholz and *E. crus-galli* (L.) Beauv are also known as Japanese millet. *Echinochloa colona* (L.) Link is regarded as the wild ancestor of the cultivated cereal crop *E. frumentacea*.

<sup>b</sup> Because of the close relationship between *Echinochloa* spp. and *Panicum* spp., it is possible that hitherto undiscovered steroidal saponins may cause crystalloid cholangiohepatopathy resulting in a secondary photosensitisation.

**Table 8**

C1 insects that have been implicated in suspected primary phototoxicity (poor or inconsistent field evidence, but experimental feeding has produced photosensitisation OR potential phototoxin isolated).

Insect	Experimental feeding resulted in photosensitisation	Phototoxin(s)	Citations
<i>Coccinella septempunctata</i> Linnaeus, 1758 (seven-spotted ladybird) <sup>a</sup>	Yes	Unknown	Ferrer et al. (2007)
<i>Aphis craccivora</i> C.L. Koch, 1854 (cowpea aphid)	Not done	Xantho-, rhodo- and erythroaphins (perylenequinones)	(Banks and Cameron, 1972; Bowie et al., 1966; Brown, 1975; Todd, 1963)

<sup>a</sup> In the report by Ferrer et al. (2007), there is evidence that macerated ladybird larvae and chrysalises that were dosed to a sheep caused photosensitisation. It is conceivable that the ladybird larvae, which feed on cowpea aphids, could contain perylenequinones derived from the latter. Apparently, Ferrer et al. (2007) did not attempt the feeding of aphids (only) to a sheep.

**Table 9**

Phototoxins that have been isolated (D1) and that experimentally reproduce photosensitisation (D2) but where no field evidence in farm animals has been reported.

Phototoxin	Phototoxin experimentally reproduced photosensitisation(s)	Citations
Perloine from <i>Lolium perenne</i> L. (perennial ryegrass) and <i>Schedonorus arundinaceus</i> (Schreb.) Dumort. (tall fescue)	Yes	(Aasen et al., 1969; Cao et al., 2008, 2017; Cunningham and Clare, 1943)
Pheophorbide a (chlorin catabolite of chlorophyll a)	Yes	(Clare, 1955; Lohrey et al., 1974; Tapper et al., 1975)
Perylenequinone mycotoxins, e.g. hypericin <sup>a</sup> , cercosporin <sup>b</sup> , phleochrome <sup>c</sup> and altretoxins <sup>d</sup> , as well as pigments produced by <i>Elsinoë</i> spp.	No	(Daub et al., 2005; Kusari et al., 2008; Podlech et al., 2014; Tabuchi et al., 1994; Weiss et al., 1957; Yoshihara et al., 1975)
Anthraquinone mycotoxins, e.g. macrosporin <sup>e</sup>	No	Trigos et al. (2011)

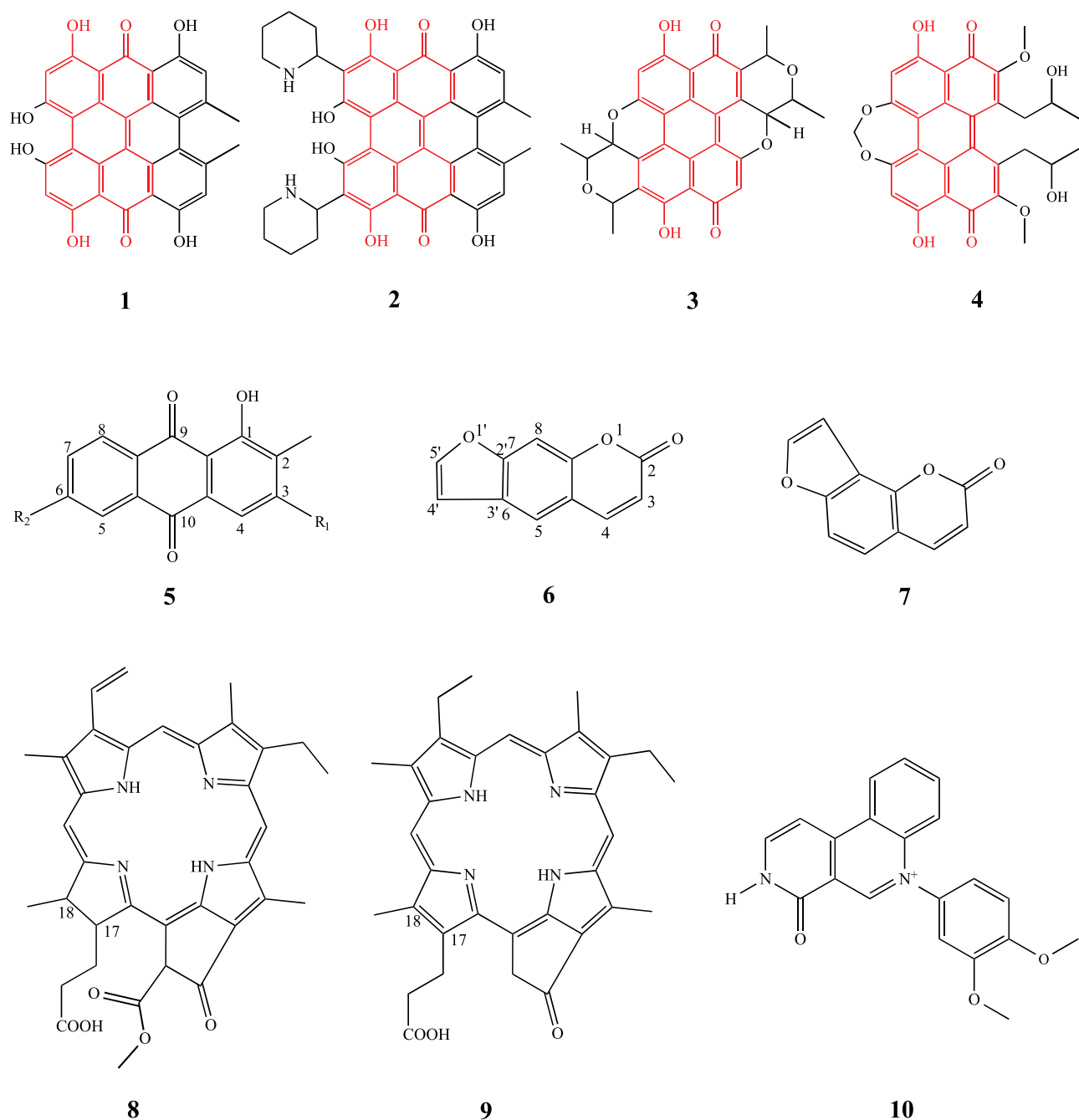
<sup>a</sup> Produced by an endophyte *Thielavia subthermophila* Mouch., isolated from *Hypericum perforatum* (Kusari et al., 2009).

<sup>b</sup> Certain fungi infecting common pasture plant species can produce mycotoxins. Cercosporin is produced by *Cercospora zebrina* Pass., the cause of cercospora leafspot of white clover (Lynch and Geoghegan, 1977), and *Cercosporidium (Scoleotrichum) graminis* (Fuckel) Deighton, the cause of brown leaf spot or leaf streak of cocksfoot (orchardgrass; *Dactylis glomerata* L.) (Latch and Wenham, 1958; Tabuchi et al., 1994), perennial ryegrass (*L. perenne*), prairie grass (*Bromus willdenowii* Kunth), timothy (*Phleum pratense* L.), and tall fescue (*S. arundinaceus*) (Harvey and Harvey, 2009).

<sup>c</sup> Produced by *Cladosporium phlei* (Gregory) de Vries, a pathogen of timothy grass (Yoshihara et al., 1975).

<sup>d</sup> Produced by ubiquitous *Alternaria* spp. (Podlech et al., 2014).

<sup>e</sup> Macrosporin is produced by certain *Cladosporium* spp., *Alternaria* spp., and several other fungi (Trigos et al., 2011).



**Fig. 1.** The structures depicted are as follows: Top row, perylenequinones (basic structure in red), comprising hypericin (1) from *Hypericum* spp., fagopyrin (2) from *Fagopyrum esculentum*, erythroaphin (3) from the cowpea aphid *Aphis craccivora*, and the mycotoxin cercosporin (4). Middle row shows an aglycone anthraquinone (5) (for rubiadin,  $R_1 = \text{OH}$ ,  $R_2 = \text{H}$ ; for soranjidiol  $R_1 = \text{H}$ ,  $R_2 = \text{OH}$ ), the linear furanocoumarin psoralen (6) (two other important linear furanocoumarins are xanthotoxin [methoxy group at position 8] and bergapten [methoxy group at position 5]), and the angular furanocoumarin angelicin (7). Bottom row shows the two chlorophyll derivatives, pheophorbide *a* (8, note the single bond at 17–18 making it a chlorin), and phytylporphyrin (9, porphyrins have a double bond at 17–18), as well as the alkaloid perlorline (10). Phytylporphyrin (phyloerythrin) is the phototoxin in secondary photosensitisations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

anthraquinones have recently been reviewed (Duval et al., 2016) and those used for cegadera extracts have been described (Barrera Vázquez et al., 2014; Barrera Vázquez et al., 2015; Núñez Montoya et al., 2003; Núñez Montoya et al., 2005).

In any analysis for potential phototoxins in plants, however, efforts need to be made to remove chlorophyll from extracts. If characteristic absorption spectra of chlorin derivatives are discovered (Campbell et al., 2010), further work to correlate the action spectra in serum or tissues of animals experimentally photosensitised, will be necessary.

The phototoxic anthraquinones soranjidiol (red) and rubiadin

(yellow) have absorption maxima at the interface of the UV-C and UV-B (~280 nm) and at 410–420 nm (visible light) (Caro et al., 2012; Comini et al., 2011; Núñez Montoya et al., 2005). Hypericin (perylenequinone) has absorption maxima at 236 and 592 nm (Draves and Walker, 2000). Furanocoumarins have absorption maxima within the UV-A range (320–380 nm) (Diawara and Trumble, 1997).

## 12. Anthraquinones

Several hundred natural anthraquinone compounds are known and

they differ in the nature and positions of substituent groups. Aglycone and glycosidic anthraquinones are mainly found in the plant families Rubiaceae, Polygonaceae, Rhamnaceae, Fabaceae, Liliaceae, Bignoniaceae and Pedaliaceae, certain insects (e.g. cochineal), and lichens, as well as some filamentous and even endophytic fungi (Caro et al., 2012; Gessler et al., 2013). The ones of interest here are the hydroxyanthraquinoid (HAQN) compounds, i.e. the basic molecular structure comprises a 9,10-anthraquinone (also referred to as 9,10-anthracenedione or 9,10-dioxoanthracene) with any number  $n$  of hydrogen atoms replaced by hydroxyl (-OH) or methyl groups (Caro et al., 2012) (Fig. 1). The HAQN absorb light and are yellow to brown to red – they have the same basic chromophore which consists of the two carbonyl groups in conjugation with two carbon-carbon double bonds and their colour depends on the position and number of hydroxyl substituents (Caro et al., 2012; Harborne, 1984). They generally make little contribution to the colour of plants as other pigments mask them (Harborne, 1984). Many of these pigments possess natural fluorescence (He et al., 2009). Natural HAQN pigments possess a broad range of anti-inflammatory, anti-cancer, antiviral, antimicrobial, antiparasitic, insecticidal, astringent and purgative activities (Caro et al., 2012; Gessler et al., 2013). Many HAQN compounds found in the Fabaceae (e.g. *Cassia* and *Senna* spp.), Liliaceae (e.g. *Aloe* spp.), Polygonaceae (e.g. *Rumex* spp.), and Rhamnaceae (e.g. cascara sagrada, the dried bark of *Rhamnus purshiana* DC.) have hydroxyl groups at positions 1 and 8. These aglycone HAQNs, as well as their glycosides, plus numerous other molecular combinations, such as dianthrone (sennosides), are valued in traditional folk medicines for their laxative, purgative and skin healing properties (Dave and Ledwani, 2012). The cegadera aglycone anthraquinones, on the other hand, lack the position 8 hydroxyl, but have one either at position 3 (rubiadin) or 6 (soranjidiol), as well as a methyl group at position 2 (Núñez Montoya et al., 2005). The cegadera HAQN are highly lipophilic favouring absorption from the small intestine. In contrast, the *Cassia* and *Senna* HAQN and their glycosides are metabolised differently being processed in the colon (hence their use as laxatives) before faecal excretion (Dave and Ledwani, 2012; Núñez Montoya et al., 2008; Sendelbach, 1989).

In New Zealand, plants that contain one or more of the HAQNs, rubiadin, rubiadin 1-methyl ether, soranjidiol, xanthopurpurin, purpurin, pseudopurpurin, alizarin and lucidin, include several *Galium* (the cleavers or bed straw) and *Coprosma* spp., plus *Sherardia arvensis* (field madder) (all in the Rubiaceae) (Burnett and Thomson, 1968; Caro et al., 2012; Morimoto et al., 2002; Thomson, 1971). On the other hand, *Rumex obtusifolius* (broad-leaved dock, Polygonaceae), a common weed in dairy pastures, contains the HAQNs aloe-emodin, emodin, rhein, chrysophanol, physcion (= parietin), obtusifolate A and B, as well as 1,3,6-trihydroxy-anthraquinone (demethylmacroporin) (Fairbairn and El-Muhtadi, 1972; Ibáñez-Calero et al., 2009; Khabir et al., 2017; Thomson, 1971). Numerous HAQN anthraquinones are found in fungi (Gessler et al., 2013).

### 13. Perylenequinones

Apart from hypericin, pseudohypericin, and fagopyrin and its derivatives (Benković et al., 2014; Kitanov, 2001), certain mycotoxins (Table 9), insect pigments (Table 8) and humic substances (Sato and Kumada, 1967) (see below) are perylenequinones. As far as I'm aware, there is no evidence of phytophoto-contact dermatitis from perylenequinone-containing plants (Henry, 1922; Kingsbury, 1964).

### 14. Furanocoumarins

Apart from those mentioned in Table 3, several other plants belonging to the Apiaceae and Rutaceae contain one or more furanocoumarins. A number have been incriminated in human cases of phytophoto-contact dermatitis. These include giant parsnip and cow parsnip (*Heracleum* spp.; furanocoumarins isolated include bergapten,

psoralen, xanthotoxin, imperatorin, and angelicin) (Baker et al., 2017; Camm et al., 1976), fennel (*Foeniculum vulgare* Mill.; bergapten, psoralen), dill (*Anethum graveolens* L.; bergapten), carrot (*Daucus carota* subsp. *sativus* (Hoffm.) Schübl & G. Martens; peucedanin), *Angelica* spp. (angelicin, bergapten), common rue (*Ruta graveolens* L.; psoralen, bergapten), and *Citrus* spp. (e.g. limes, bergamot orange, grapefruit, Earl Grey tea; bergamottin, bergapten) (Gawkrodder and Savin, 1983; Murray et al., 1982; Pathak et al., 1962; Peroutka et al., 2007). The cultivated tomato, *Lycopersicon esculentum* Mill. (Solanaceae) contains bergapten (Méndez and Brown, 1971; Murray et al., 1982). The author is unaware of any reports of farm livestock photosensitisation associated with these, apart from parsley (*Petroselinum crispum* (Mill.) Fuss) photosensitisation in ostriches and ducks (Perelman and Kuttin, 1988). Parsley contains bergapten, xanthotoxin and oxypeucedanin (Chaudhary et al., 1986; Murray et al., 1982). Conceivably, because of the documented human cases of phytophoto-contact dermatitis from furanocoumarin-containing plants, the possibility that certain of these plant species may evoke similar reactions in farm animals should be considered (Ivie, 1978).

In New Zealand, other plants that could potentially evoke photosensitisation because of furanocoumarins are hemlock (*Conium maculatum* L.; bergapten) (Murray et al., 1982), common vetch (*Vicia sativa* L. Fabaceae; bergapten, xanthotoxin) (Southon, 1994), and various *Pitopsisporum* spp. (Pitopsisporaceae, e.g. *P. eugenoides*, *P. tenuifolium*; bergapten) (Murray et al., 1982).

Amongst the natural furanocoumarins, psoralen has the highest photodynamic activity, followed by xanthotoxin, and bergapten (these are linear furanocoumarins), while the angular furanocoumarin, angelicin is weaker (Murray et al., 1982). The not inconceivable possibility that different phototoxic furanocoumarins, present in the same plant, could play an enhancing or synergistic role in animal or human photosensitisation, has not been investigated.

### 15. Chlorophyll derivatives

Apart from phytoporphyrin, the phototoxin in secondary photosensitisation, pheophorbide *a* (Table 9), a chlorin derivative of chlorophyll breakdown, has been shown to be the phototoxin in cases of pseudoporphyria in humans (Jitsukawa et al., 1984; Rossi et al., 2015; Zhao et al., 2016). As far as I know, there are no reports of primary photosensitisation in livestock associated with elevated concentrations of pheophorbide in the blood or tissues of farm livestock. This is surprising considering that chlorophyll is the major photodynamic pigment associated with green plants in the diet.

### 16. Miscellaneous

There are a large number of compounds of plant, fungal or cyanobacterial origin that fluoresce when irradiated with light in the UV or visible range. In addition to those mentioned already, these include certain carotenes, phenols, amino acids and proteins, anthraquinones, cinnamic acid derivatives, coumarins, flavones, riboflavin (vitamin B<sub>2</sub>), purines, tetrapyrroles (such as protochlorophyllide, as well as pheophorbide and other chlorophyll derivatives) (Campbell et al., 2010; Tønnesen et al., 2013), phycocyanins and phycoerythrins (the two main groups of phycobiliproteins, which are water soluble fluorescent, light-harvesting chromoproteins derived from cyanobacteria and other algae) (Tønnesen et al., 2013), certain alkaloids (e.g. ergotamine, peroline, quinine, solanine), aureomycin, and rotenone, as well as substances produced when plants are infected by certain fungi or viruses (Goodwin, 1953). Many of these compounds are powerful generators of singlet oxygen and other reactive oxygen species. Even humic compounds, which are supramolecular associations of low-molecular-mass organic molecules possibly derived from soil fungi, dissolved in fresh water, have been shown to generate singlet oxygen (Knox and Dodge, 1985; Tønnesen et al., 2013; Valmaseda et al., 1989). Another group



includes the bacteriochlorins, such as tolyporphrin (Prinsep et al., 2017), derived from cyanobacteria. For most of these compounds, however, data concerning their possible phototoxicity (i.e. type I or type II or both reactions) in animal tissue systems is lacking.

The level of singlet oxygen in serum can be used as a measure of the photosensitising potential; serum from affected animals have levels significantly higher than normal controls (Tønnesen et al., 2010). Unfortunately, though, such measurements provide no indication as to the nature of the endo- or exogenous phototoxin.

Flavonoids absorb various wavelengths of light (Buer et al., 2010) and have fluorescence properties (Monago-Maraña et al., 2016). Some, such as rutin, can also demonstrate phototoxicity (Wilhelm et al., 2001). Whether or not flavonoids play any causative or enhancing role in photosensitisation will depend on *in vitro* testing for type I and type II phototoxicity, animal dosing trials, and correlation of absorption and action spectra.

## 17. Conclusions

In this paper, an unambiguous classification of the mechanisms of photosensitisation based on Clare (1952) is proposed. The four categories are primary, secondary, endogenous, and idiopathic.

Next, with respect to primary phototoxic plants and other agents, a classification of confidence rankings based on weight of evidence, is presented. The confidence ranks range from A5 to D1. According to this classification, there are at least seventeen plants ranked as A5 (definite phototoxicity with a maximum weight of evidence; Table 3), five as A2 (field evidence and positive results on experimental feeding or dosing; Table 4), three as B2 (field evidence and either positive results with experimental feeding/dosing or phototoxin(s) isolated; Tables 5 and 6), eight as B1 (field evidence only; Table 7), two C1 insects (poor or inconsistent field evidence, positive results following experimental feeding of the seven-spotted ladybird, or the cowpea aphid containing potentially phototoxic perylenequinones; Table 8), two D2 phototoxins (with no field evidence in farm animals, but experimental evidence; Table 9), and two D1 groups of mycotoxins (no field evidence, and no experimental evidence at this stage; Table 9).

To date, there are representatives of only four classes of compounds that are known to be phototoxic to farm animals. These are perylenequinones, aglycone anthraquinones, linear furanocoumarins, and derivatives of chlorophyll (pheophorbide *a* and phytoporphyrin). Of these, the furanocoumarin-containing plants are the only ones that are sometimes implicated in cases of phytophoto-contact dermatitis.

In most plants associated with primary photosensitisation, more than one phototoxin from the same class of compounds is often present. Examples include the perylenequinones, namely hypericin and pseudohypericin in *Hypericum* spp. (Kitanov, 2001; Vandenbergaeerde et al., 1998), and fagopyrin and various analogues in *Fagopyrum* spp. (Benković et al., 2014), the anthraquinones such as rubiadin and others in *Heterophyllaea* spp. (Dimmer et al., 2017; Núñez Montoya et al., 2006), as well as the various furanocoumarins in phototoxic plants belonging to the Apiaceae, Fabaceae and Rutaceae families (Table 3). Whether or not multiple phototoxins with a similar structure and biological behaviour, present in the same plant at the same time, exert any complementary or synergistic role in animal or human photosensitisation has not been investigated.

A major relatively recent breakthrough has been the discovery of phototoxic aglycone anthraquinones in *Heterophyllaea* spp. This has opened the possibility that other anthraquinone-containing plants may be phototoxic to farm animals. The search for data on plant phytochemistry has serendipitously revealed that phototoxic anthraquinones (Fan et al., 2008) are present in alligator weed (*Alternanthera philoxeroides*), which has long been associated with photosensitisation in cattle in New Zealand and Australia (Anonymous, 1989; Bourke and Rayward, 2003). To my knowledge, no feeding or dosing trials have been performed with alligator weed, so I classify it as B2. It would be

worth testing *Froelichia humboldtiana* (A2), another representative of the Amaranthaceae family, for phototoxic anthraquinones.

Other A2 plants that would benefit from a targeted phytochemical analysis aimed at the *in vitro* discovery of type I and/or type II photosensitisation mechanisms include the *Brassica* spp. and *Biserulla pelecinus*.

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## Conflicts of interest

I declare that I have no conflicts of interest.

## Ethical statement

I declare that no animal or human was harmed in any way. This paper does not report any experimental findings.

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