Effects of *Hypericum perforatum* (St. John's wort) on animal health and production

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Summary

***Hypericum perforatum* and related species contain a mixture of photodynamic compounds represented by hypericin. Visible wavelengths of light energize hypericin and make it toxic to cell membranes. This effect occurs in exposed non-pigmented skin areas on animals that eat wort. Photosensitization is the skin inflammation that follows. Hypericin can enter the brain and exert a stimulant effect upon behaviour, and an altered sense of temperature perception. In the peripheral nervous system hypericin alters heart, blood vessel, and intestinal function by inhibiting a catechol enzyme. A transient elevation of adrenaline and noradrenaline follows. Sucking young can ingest hypericin in their mother's milk. Chronic hypericin ingestion causes weight loss, failure to gain weight, reduced milk and wool production, and reduced reproductive performance. Wort infested pastures can halve per hectare carrying capacity, and some livestock will die because of grazing wort. Horses are more susceptible to hypericin toxicity than cattle, cattle more than sheep, and sheep more than goats, probably because of differences in liver enzyme metabolizing systems. The presence of skin pigment or a thick wool covering will reduce the photosensitizing effect of hypericin. The other effects of hypericin exert themselves regardless of sunlight exposure. Annual animal production losses on wort infested pastures in New South Wales can approximate $22.5 million.**

Introduction

The ingestion of *Hypericum perforatum*, and related species of wort, by livestock will inevitably result in significant animal health problems and production losses. All parts of these plants contain a mixture of polyhydroxyphenolic compounds typically represented by hypericin (see Figure 1), a fluorescent pigment derived from the dianthrone compound helianthrone (Kingsbury 1964, Cheeke and Shull 1985).

Photosensitizing effect of hypericin

The presence of both hydroxyl and methyl side groups on the hypericin molecule endows it with cell membrane interactive properties, that is, a part of the molecule is hydrophilic and another part is lipophilic. In addition, the presence of alternating double bonds throughout the molecule, and two oxygen side groups, which also involve double bonds, bestows a photodynamic potential upon the molecule (Mazur and Harrow 1971). Wavelengths of 580 nm (range 540–590 nm) will significantly energize hypericin (Hudson and Towers 1994). This is visible light, not ultraviolet. The electrons in the oxygen side groups rise to orbits further away from the nuclei of the atoms. Consequently there is less force holding the electrons, and 'singlet' oxygen is produced. In this energized state hypericin is highly toxic to many cell membranes, and will destroy cells. Thus, hypericin can cause photosensitization, a very disfiguring and painful skin disorder. The hydrophilic nature of the hypericin molecule will guarantee its rapid absorption from the gastrointestinal tract, and its rapid distribution to the peripheral circulation. The liver will not have sufficient time to detoxify it. Hypericin, arriving in the blood stream at bare non-pigmented skin sites, may become energized by bright sunlight falling on these sites. Consequently the photo-energized hypericin interacts with the membranes of cells in the immediate vicinity, and causes them to rupture. This establishes a localized inflammatory cascade.

St. John's wort is only one of many plants that can cause 'primary' photosensitization. These are plants that contain substances that are photodynamic of themselves. Another group of plants can cause 'secondary' photosensitization. They contain substances that are hepatotoxic (cause liver damage). This effect will allow normal, but potentially photodynamic, metabolites of chlorophyll (such as phylloerythrin) to circulate in the bloodstream in large amounts (Blood and Radostits 1989). Some other primary photosensitizing plants contain compounds similar to hypericin. Fagopyrin in buckwheat (*Fagopyrum* sp.) is one example. Others, such as parsnips and celery, contain furocoumarins and phytoalexins. Some fungal infestations in these plants will generate phytoalexins (Kellerman *et al.* 1988). Common pasture species, such as lucerne and burr clover, and common fodder species, such as green oat crops, are also sporadically involved in outbreaks of photosensitization (C.A. Bourke unpublished data). Possibly these have a 'primary' causality as well. Some veterinary chemicals, such as the drench phenothiazine, and the tetracycline antibiotics, are also potential primary photosensitizers.

Other effects of hypericin

Hypericin does not require photoenergization to cross either the blood brain barrier or the blood mammary gland barrier. Its dual hydrophilic and lipophilic properties enable it to enter the central nervous system (brain and spinal cord), and the milk supply (in lactating animals). In the brain small amounts of hypericin have a stimulant or antidepressant effect (Hudson and Towers 1994). Conversely large amounts would be depressant. It is also likely that hypericin can affect the temperature control centre in the brain. This can cause an exaggerated perception of 'cold' or 'hot', or an abnormal elevation in body temperature (Everist 1981, Seawright 1989). Hypericin can exert an inhibitory effect on the enzyme catechol-o-methyl transferase (Seawright 1989). This action is not light dependant. A consequence of this effect is adrenaline and noradrenaline accumulation. The sympathomimetic activity that follows can involve the heart, blood vessels and smooth muscle systems (e.g. the intestines). Typically there is vasoconstriction in many body areas, but a rush of blood to the muscles. Initially there is an increase in heart rate, cardiac output, and blood pressure. Intestinal effects may sometimes result in diarrhoea. The overall effect on the animal is to switch it into an agitated mental state akin to the 'flight or fight' response.

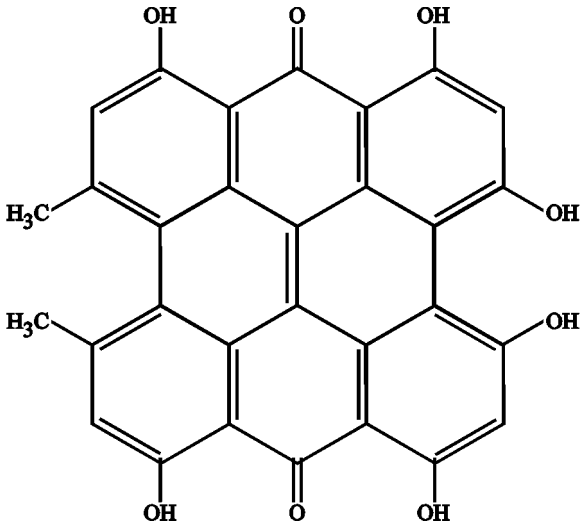

Figure 1. Chemical structure of hypericin.

The composite clinical picture

The clinical effect of hypericin toxicity in livestock will be a composite of its photosensitizing effect, its brain effect and its sympathomimetic effect. The complete clinical picture is as follows:

- Severe erythema (reddening) of non-pigmented and unprotected skin sites. Eventually there is swelling, exudation (weeping) and scab formation at these sites. Associated intense pruitis (itch) will exacerbate the inflammatory process by encouraging the affected animal to rub the lesions (wounds) until they are raw. Lips, nose, face, eyelids, and ears are commonly affected. The top line of the body, the udder, and the eyes, both around them (conjunctivitis), or over the surface of them (keratitis), are affected sometimes.
- There may be hyperactivity with mania, or conversely marked depression. Affected animals may have an elevated temperature and consequently seek relief in water. Conversely they may show a bizarre sensitivity to water, be it a creek crossing or a plunge dip.
- Affected animals may be apprehensive, have an increased heart rate, and an increased respiration rate. Some may also develop diarrhoea.
- The milk production of lactating animals may decline or stop altogether. Pregnant animals may abort.
- Affected animals will lose weight, or fail to gain weight. Young animals will be more severely affected than older ones.
- Death may occur in some animals. This may be a direct result of starvation, or because of secondary disease problems (due to their debilitated condition). Some affected animals may accidentally drown.

Effect of hypericin on animal production

The animal production loss associated with grazing St. John's wort pastures includes the following; weight loss and failure to gain weight associated with a reduction in eating ability or interest in eating, there will be less wool produced in sheep and less milk produced in sheep and cattle, fewer lambs and calves will be born alive and less will survive to weaning and finally, fewer ewes or cows will be sufficiently heavy or healthy to conceive in the first place. An additional loss on wort dominant pastures is reduced carrying capacity. In New South Wales wort infestation covers approximately 250 000 ha of higher rainfall, potentially highly productive, tablelands and slopes, hill country (Campbell and Watson 1994). The following is a reasonable prediction of the annual production loss expected. If a merino wether enterprise, with a potential carrying capacity of five dry sheep equivalents (DSE) per hectare, is used as a model, the reduction in carrying capacity would be 2.5 DSE (Campbell and Watson 1994). For an anticipated annual gross return from wool of $30 per DSE, the initial loss from reduced carrying over the area of the infestation would be $18.75 million per annum. Assuming it is a conventional livestock enterprise, managed by an operator with average skills, the additional livestock death and production losses that could be anticipated from grazing the wort would be at least another 20% (i.e. $3.75 million). The total loss for the area of the infestation would be $22.5 million per annum .

Sensitivity of livestock to hypericin

Photodynamic agents can cause signs of photosensitization in less than 24 hours. They will continue to cause these signs for as long as they are ingested and the animal is exposed to bright sunlight. The presence of pigment in the skin, or the presence of an opaque barrier to sunlight, will significantly reduce the photosensitizing potential of hypericin. Neither skin pigments, nor wool and hair coverings, will prevent the other physiological effects of hypericin. There is an animal species variation in sensitivity to hypericin. This occurs with other primary photosensitizers, such as phenothiazine, as well. Liver enzymes present in some animal species are probably much more efficient at metabolizing these compounds (Clarke and Clarke 1978). Thus, horses are the most sensitive to hypericin and goats the least. Cattle and sheep lie between these two extremes. Cattle are more sensitive than sheep, but because many breeds of cattle are fully coloured (pigmented), this difference in sensitivity may not be readily appreciated.

Plant variation in hypericin content

Hypericin toxicity can occur at any stage of the plant's growth, and by feeding any product made from the plant, including hay. Hypericin has a very stable chemical structure. Hypericin levels in the narrow leaved varieties of wort are up to four times as great as those in the broad leaved varieties (Southwell and Campbell 1991). The distribution of hypericin in the broad leaved plant is as follows: stems 40–120 mg kg^{-1}, leaves 290–380 mg kg^{-1}, flowers 2150 mg kg^{-1}, and fruits 730 mg kg^{-1}. Photosensitization can occur in cattle after the ingestion of only 1% of their body weight (as fresh green plant) in one day. In sheep the ingestion of 5% of their body weight is required (Kingsbury 1964). St. John's wort has a perennial growth habit and a tendency to grow throughout all seasons of the year. This means that paddocks infested with wort are always potentially toxic to livestock. Low growing non-flowering green stems develop during late autumn and winter, and fresh, erect growing woody, flowering stems develop during spring and early summer. These stems die and brown off during late summer and early autumn. All this plant material, at all these stages of growth, contains toxic amounts of hypericin. The greatest risk to livestock is from late autumn to early spring, because the succulent fresh new growth stage is more palatable then the woody flowering and senescing stage that follows.

Conclusion

All livestock groups forced to graze pastures dominated by St. John's wort will inevitably experience health problems and production losses. This will be despite the animal species used or the colour of the breed selected. Hypericin toxicity is an inevitable outcome when wort infested pastures are grazed by livestock. The challenge to management is to reduce the extent to which this toxicity impinges on the performance of a livestock enterprise.

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