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A Review of the Hepatotoxic Plant *Lantana camara*

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Lantana (*Lantana camara* Linn) is a noxious weed that grows in many tropical and subtropical parts of the world. Ingestion of lantana foliage by grazing animals causes cholestasis and hepatotoxicity. Both ruminants and nonruminant animals such as guinea pigs, rabbits, and female rats are susceptible to the hepatotoxic action of lantana toxins. The hepatotoxins are pentacyclic triterpenoids called lantadenes. Molecular structure of lantadenes has been determined. Green unripe fruits of the plant are toxic to humans. *Lantana* spp. exert allelopathic action on the neighboring vegetation. The allelochemicals have been identified as phenolics, with umbelliferone, methylcoumarin, and salicylic acid being the most phytotoxic. In addition to phenolics, a recent report indicates lantadene A and B as more potent allelochemicals. Management of lantana toxicosis in animals is achieved by drenching with activated charcoal and supportive therapy. Recent reports on the bilirubin clearance effect of Chinese herbal tea Yin Zhi Huang (decoction of the plant Yin Chin, *Artemisia capillaries,* and three other herbs) or its active ingredient 6,7-dimethylesculetin, in jaundice are very exciting and warrant investigations on its, possible, ameliorative effects in lantana intoxicated animals. Research is being conducted on new drug discovery based on natural products in different parts of the lantana plant.

Keywords Cholestasis, Hepatotoxicity, Hepatotoxins, Lantana, *Lantana camara*, Lantadenes, Pentacyclic Triterpenoids, Toxins

I. INTRODUCTION

Lantana camara Linn. (family: Verbenaceae), an ornamental shrub, has spread as an intractable weed in many parts of the world (Sharma et al., 1988b). Some other important species of the genus *Lantana* are *L. indica*, *L. crenulata*, *L. trifolia*, *L. lilacina*, *L. involuerata*, and *L. sellowiance* (Sharma et al., 1981b). The plant has curved prickles on its branches, grows to a height of 2–3 m, and spreads its branches to cover an area of about 1 m^2 (Sharma et al., 1981b). Mature leaves are rough, cause irritation to the skin when touched, give off an unpleasant odor, are 5–9 cm long, ovate or oblong, cuneate, rounded or cordate at the base and crenate and rugose above (Sharma et al., 1981b). The ingestion of plant foliage by grazing animals causes hepatotoxicity and is an important cause of livestock morbidity and mortality in lantana-infested regions (Sharma and Makkar, 1981; Sharma et al., 1979). The flowers are subumbellate when young. The fruit is a drupe, 0.5 cm in diameter, greenish in early stages and dark blue on ripening (Sharma et al., 1981b). Ripe fruits are sweet to taste and are eaten by birds and children (Sharma et al., 1979; Chopra et al., 1965). In India, the plant starts flowering in April–May and fruiting continues till November–December (Sharma et al., 1981b).

The genus *Lantana* contains many species that are native to the Americas and Africa, and has become naturalized as a noxious weed in tropical, subtropical, and warm temperate countries (Day et al., 2003). *Lantana camara* has been found in nearly

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50 countries and is the principal weed in 12 countries (Holm et al., 1979; Ghisalberti, 2000). It is a serious weed spreading over Australia, Asia, Africa, South America, and North America (Table 1). Strategies for the control of lantana have been reviewed in a recent monograph by Day and coworkers (2003).

Lantana horrida, one of the noxious plant species on rangelands in the southwestern United States, has been mapped using remote sensing technique (Everitt et al., 1995). *Lantana camara* is one of the five weeds covering 60% of the pastures in Central Queensland, Australia (Anderson et al., 1983), and has been listed as one of the nine declared noxious weeds of the north coast of Australia (Dayson, 1989). Dry rainforests (73%) in Forty Mile Scrub National Park and in adjacent Savanna Woodland, Queensland, Australia, have been invaded by *L. camara,* causing a decline in the species richness, besides increasing flammability of the fire-sensitive dry rainforest vegetation (Fensham et al., 1994; Fensham, 1996). Similarly, the invasion of the dry rainforest ecotones by *L. camara* in the gorges of Macleay River, New South Wales, Australia, has been promoted by burning, biomass removal, soil sclarification, NPK fertilizers, and cattle grazing (Gentle and Duggin, 1997). Degradation of beachfront

TABLE 1
Distribution and impact of lantana in different regions of the world

Plant	Place/Country	Impact	References
L. camara Linn.	Central Queensland, Australia	Replaced 60% of the pasture lands	Anderson et al. (1983)
	North coast and Mt. Abbot (near Bowen) Queensland, Australia	Noxious weed	Dayson (1989)
	Forty Mile Scrub National Park and Savanna woodland, Queensland, Australia	Replaced 73% of the dry rain forests causing decline in species richness and increase in flammability of the vegetation.	Fensham et al. (1994), Fensham (1996)
	Gorges of Macleay River, NSW, Australia	Invasion of dry rain forest ecotones	Gentle and Duggin (1997)
	East coast of Queensland from Gold coast to Thursday Island, Australia	Degradation of beachfront vegetation	Batianoff and Franks (1997)
	South-western cape, Cape of Good Hope, Pietermartizburg, South Africa	Decline in diversity of invertebrate population due to invasion of indigenous vegetation	Samways et al. (1996), Stirton (1987), Taylor (1974)
	Galapagos Islands, Equador, Juan Fernadez islands	Threat to indigenous ecosystems	Mauchamp (1997), Swarbrick (1989)
	Chile and Pacific islands		Swenson et al. (1997), Thaman (1974)
	French Polynesia	Weed	Florence et al. (1983)
	LaReunion, Mascarene Islands (Indian Ocean)	Invasion of primary forests	MacDonald et al. (1991)
	Guam	Noxious weed	McConnell and Munniappan (1991)
	Benakat, South Sumatra	Invasion of industrial forest plantation	Pratiwi and Nazif (1989)
	Bandung Uttara forests district, West Java	Noxious weed invading *Pinus merkusii* stands	Endom and Soenarno (1989)
	Western Ghats, South India	Invasive weed	Muniappan and Viraktamath (1993)
	Kumaun (U. P. hills), India	Replaced *Quercus leucotrichphora* and *Pinus roxburghii* forests	Bhatt et al. (1994)
	Tamil Nadu, India	Invaded teak plantations	Clarson and Sudha (1997)
	Headwaters region of Garhwal (U. P. hills), India	Loss of palatable and economically important spp. and change in nutrient composition of the soil	Rajwar and Kilmartin (1998)
L. horrida	Rangelands in southwestern USA	Noxious weed	Everitt et al. (1995)
L. indica Roxb.	Fields and dry deciduous forests of Sagar, Madhya Pradesh, India	Invasive weed	Shrivas and Bajpai (1988)
L. rugosa	Northern Orange Free State, South Africa	Weed	Fuls et al. (1993)

vegetation along the east coast of Queensland from Gold Coast to Thursday Island has also been attributed to the invasion by *L. camara* (Batianoff and Franks, 1997). *Lantana camara* is an aggressive woody species that escapes from gardens, displacing indigenous vegetation, and has led to a decline in the diversity of the invertebrate population at different locations in South Africa (Samways et al., 1996; Stirton, 1987; Taylor, 1974). The plant can propagate rapidly by means of stumps or cuttings, but the natural propagation appears to be from seeds disseminated by birds through droppings or through the feces of moving flocks of sheep and goats (Gujral and Vasudevan, 1983; Sharma et al., 1988b).

Weeds are known to inhibit the growth of neighboring vegetation due to release of toxins by seeds, living plants, and their residues (Rice, 1979). The phenomenon known as allelopathy is one of the important factors contributing to predominance of lantana in various ecosystems (Achhireddy et al., 1984; Putnam and Duke, 1978; Ferguson and Rathinasabapathi, 2003). The generally suppressive effect of lantana on a wide range of native species in Australia has been documented by Hughes (2006). The allelopathic or phytotoxic effects of lantana extracts are summarized in Table 2. The allelochemicals have been identified as phenolics, with umbelliferone, methylcoumarin, and salicylic acid being the most phytotoxic (Singh et al., 1989; Jain et al., 1989). A recent study by Kong et al. (2006) shows that the growth of the aquatic weed *Eichhornia crassipes* and of the alga *Microcystis aeruginosa* is inhibited by fallen leaves of *L. camara*. Further, it was observed that the extracts of *L. camara* leaves and their fractions reduced the biomass of *E. crassipes* and *M. aeruginosa* within 7 days under experimental conditions. Two fractions with highly inhibitory activity from the extract were isolated and subsequently identified as the pentacyclic triterpenoids lantadene A (**1**) and lantadene B (**2**). Both the compounds significantly inhibited *E. crassipes* and *M. aeruginosa* growth, even at a low concentration. The authors adduced evidence that the predominant allelochemicals involved in *L. camara* against either *E. crassipes* or *M. aeruginosa* are not phenolic acids, but lantadene A and lantadene B (Kong et al., 2006). Aqueous leachates of *L. camara* inhibited the radicle growth and protein pattern of tomato (Romero-Romero et al., 2002). Extract from root, stem, and leaf of *L. camara* inhibited germination of spores of *Asterella angusts* Steph.—a liverwort. Leaf extract had maximum allelopathic effect, followed by stem and roots. It was inferred that allelochemicals are synthesized in leaf and translocated to other organs (Kothari and Chaudhari, 2001).

TABLE 2
Allelopathic action of the extracts or biomass of *Lantana* spp.

Extract	Action	Reference
Extracts of root, stem, leaf and inflorescence of *L. camara*	Inhibition of the growth of the ferns *Christella dentate* and *Cyclosporous dentatus*	Wadhwani and Bhardwaja (1981), Wadhwani et al. (1983)
Volatile constituents liberated from the leaves of *L. camara*	Inhibited the growth of rice coleoptiles and increased production of secondary roots and root hairs	Das and Pal (1972)
Leaf extract of *L. camara*	Inhibited the growth of duckweed *Lemna paucicostata*	Sutton and Portier (1989)
Boiled extracts of whole plant sample of *L. camara*	Inhibited germination of *Cicer arietinum*, delayed rice seed germination and growth of citrus root stocks	Angris et al. (1988), Prasad and Srivastava (1991), Singh and Achhireddy (1987)
The aqueous extracts of stems, seeds and flowers of *L. indica*	Inhibited the germination of seeds of *Dalbergia sissoo*	Shrivas and Bajpai (1988)
Incorporation of dried lantana shoot or root material into the soil	Caused significant reduction in milkweed vine growth	Achhireddy and Singh (1984)
Aqueous extracts of *L. camara* or its debris	Inhibition of the emergence and seedling length of spinach, rape, chinese cabbage, cucumber and chillies	Sahid and Sugau (1993)
Root exudates of *L. camara*	Inhibited growth/germination in *Abel moschus esculentus, Beta vulgaris*, *Glycine max, Lycopersicum esculentum, Raphanus sativus*	Pope et al. (1985)
Extracts of *L. camara* leaves and isolated lantadene A and B	Inhibition of growth of aquatic weed *Eichhornia crassipes* and the alga *Microcystis aeruginosa*	Kong et al. (2006)

II. NATURAL PRODUCTS FROM LANTANA

Major natural products investigated in the lantana plant belong to the group of triterpenoids (Table 3), flavonoids, iridoide glycosides, oligosaccharides, phenylpropanoid glycosides, and naphthoquinones (Table 4).

Most of the triterpenoids isolated from the leaves of *L. camara* are pentacyclic and belong to the oleane series, a few belong to the ursane and lupane series, and some have an oxide bridge from C-3 to C-25 (Table 3, Figure 1). Lantadene A (LA, **1**), lantadene B (LB, **2**), lantadene C (LC, **3**), and lantadene D (LD, **4**) are the major constituents of *L. camara* (red flower variety) leaves (Sharma et al., 1988b; Sharma and Sharma, 1989; Sharma et al., 1990; Sharma, 1991b). Reduced lantadene A (RLA, **6**) and reduced lantadene B (RLB, **7**) are the minor constituents (Sharma et al., 1991b, 1997a). Icterogenin (**8**) has been reported from the leaves and stem of *L. camara* Townswhile pricky orange (Hart el al., 1976a) but could not be detected in *L. camara* red flower variety (Sharma et al., 1991b, 1997a). Townsville prickly orange has oleanonic acid (**10**) and ursonic acid (**27**) as major constituents in its leaves and stems, while LA and LB are only minor constituents (Hart et al., 1976a). LA and LB are the major constituents of the common pink-edged red flower variety (Hart et al., 1976a). LA and LB could not be detected in *L. camara* common pink and *L. tiliaefolia* (Hart et al., 1976a; Johns et al., 1983b). Similarly, LC, RLA, and icterogenin have not been reported in the taxon common pink (Sharma and Sharma, 1989). This taxon is nontoxic and is commonly grazed upon in New Zealand, where it is most widespread (Black and Carter, 1985).

The profile of triterpenoids in the roots of *L. camara* is different from that in the leaves. Oleanolic acid is the major constituent of the roots of *L. camara* Helidon white, followed by oleanonic acid (Hart et al., 1976a). Roots of *L. indica* yielded an oleane derivative 3β-24-dihydroxyolean-12-en-28-oic acid (**9**), oleanolic acid (**5**), 24-formyl-3-oxoolean- 12-en-28-oic acid (**31**), and ursolic acid (**26**) (Singh et al., 1990, 1991). Triterpenoids isolated from the roots of Chinese *L. camara* included lantanolic acid (**37**), 22β-*O*-angeloyl oleanolic acid (**19**), 22β-*O*-senecioyl-oleanolic acid, 22β-hydroxy oleanonic acid, 19α-hydroxy-ursolic acid, and 3β-isovaleroyl-19α-hydroxy-ursolic acid (Pan et al., 1993b).

A number of flavonoids with interesting biological properties have been reported from lantana plant (Table 4, Figure 1). Apigenin (**77**), cirsilineol (**78**), cirsiliol (**79**), eupafolin (**80**), eupatorin (**81**), and hispidulin (**82**) isolated from *L. montevidensis* showed antiproliferative activity (Nagao et al., 2004). Naphthoquinones lantalucratins (**83–88**) isolated from *L. involucrate* roots showed antitumor activity (Hayashi et al., 2004).

Essential oil extracted from the leaves, flowers, stem, or aerial parts of lantana plant has also been investigated (Table 4). Citral constitutes the main compound in the essential oil of five varieties of *L. camara*, a viz. *aculeata*, *hybrida*, *flava*, *nivea*, and *mista* from Cairo (Saleh, 1974). The essential oil from the aerial parts of *L. xenica* Mold. (Verbenacea) contained (*E*)-caryophyllene as the major constituent. The minor constituents were γ-cadinene, α-pinene, ocimene, and germacrene D (Juliani et al., 2002).

III. CHEMISTRY OF LANTANA TOXINS

Chemical investigations on the nature of lantana toxins were started in early 1940s (Table 5). Louw (1943, 1948) observed that two major components of lantana leaves are LA (**1**) and LB (**2**), of which LA was toxic to sheep, while LB did not elicit any toxicity. The chemical structures of LA and LB (Figure 1) were elucidated by Barton and coworkers (Barton and de Mayo, 1954a; Barton et al., 1954, 1956). In a comparative study of triterpenes of different taxa of *L. camara* in Australia, it was observed that in the taxa toxic to livestock LA and LB were present as the major constituents while RLA (**6**) and RLB (**7**) were also present in minor amounts (Hart et al., 1976a, 1976b). The nontoxic taxa including Helidon white, Townsville prickly orange, and common pink either did not contain LA and LB or contained very small amounts (Hart et al., 1976a, 1976b). Heikel and coworkers (1960) reported that LA was icterogenic to rabbits. In a subsequent study, Brown and coworkers (1963) observed that chromatographically pure LA did not elicit hepatotoxicity in rabbits. Similarly, LA was found to be nonicterogenic to lambs and guinea pigs (Seawright, 1965a), but LA induced hepatotoxicity in sheep (Hart et al., 1976b). The incongruity in the observations of different research groups as regards the hepatotoxic potential of LA was ascribed to crystal polymorphism (Bernstein, 1989). Drug action and effect of xenobiotics in animals are known to be modulated by the polymorphic form of the crystalline material administered (Hilfiker et al., 2006; Vishweshwar et al., 2005, 2006). A partially purified preparation of lantana toxin, known as fraction C, isolated from *L. camara* red variety was obtained in two forms crystalline (form I) and amorphous (form II). Only form II was icterogenic to guinea pigs (Sharma et al., 1988a). LA is one of the major constituents of fraction C, and was also obtained in two polymorphic forms and only the amorphous form (form II) elicited toxicity typical of lantana poisoning in field cases (Sharma et al., 1991a; Sharma and Vaid, 1991). LA, LB, and RLA were reported to elicit hepatotoxicity typical of natural and experimental lantana poisoning on oral administration to sheep (McSweeney, 1988; Seawright and Hrdlicka, 1977). Similarly, RLA (**6**) was toxic to female rats but male rats were not susceptible to lantana toxicity (Pass et al., 1979a). However, RLA and RLB (**7**) gave no indication of causing toxicity in sheep when given at levels equivalent to the estimated content of these compounds in a toxic amount of dried plant material (Hart et al., 1976b). Because of its comparative toxicity and abundance, LA (**1**) is the most significant toxic principle in the plant, while RLA because of its low concentration in the leaves (5% of LA) and LB (**2**) because of its significantly lower toxicity are unlikely to be of much importance in poisoning of ruminants following consumption of the plant (Seawright and Hrdlicka, 1977). A third component in the mixture of LA and LB, the presence of which escaped detection

TABLE 3
Triterpenoids from lantana plant

Compound(s)	Lantana variety	Plant part(s)	Biological activity	Reference(s)
Lantadene A (**1**) (22β-angeloyloxy-3-oxoolean-12-en-28-oic acid)	*L. camara*, R *L. camara*, CPR *L. camara*, HW *L. camara*, TRP *L. camara*, MRP *L. camara*, LO *L. camara*, TPO *L. camara*, HW	Leaves, Leaves, stem Leaves, stem Leaves, stem Leaves, stem Leaves, stem Leaves, stem Roots	Hepatotoxicity, antimicrobial, antiviral, antitumor, antitubercular, allelopathy	Barton and de Mayo (1954a), Barton et al. (1956), Heikel et al. (1960), Brown et al. (1963), Brown and Rimington (1964), Hart et al. (1976a,b), Seawright and Hrdlicka (1977), Sharma et al. (1991a), Inada et al. (1995, 1997), Verma et al. (1997), Wachter et al. (2001), Kong et al. (2006)
Lantadene B (**2**) (22β-dimethylacryloyloxy-3-oxoolean-12-en-28-oic acid)	*L. camara*, R *L. camara*, CPR *L. camara*, HW *L. camara*,TRP *L. camara*, MRP *L. camara*, LO *L. camara*, TPO *L. camara*, HW	Leaves Leaves, stem Leaves, stem Leaves, stem Leaves, stem Leaves, stem Leaves, stem Roots	Hepatotoxicity, antimicrobial, antiviral, antitumor, allelopathy	Barton et al. (1954), Brown et al. (1963), Brown and Rimington (1964), Hart et al. (1976a,b), Seawright and Hrdlicka (1977), Sharma et al. (1987), Inada et al. (1995, 1997), Verma et al. (1997), Kong et al. (2006)
Lantadene C (**3**) (22β-(S)-2′-methylbutanoyloxy-3-oxoolean-12-en-28-oic acid)	*L. camara*, R *L. camara*, SR *L. camara*, BR	Leaves Leaves, stem Leaves, stem	Hepatotoxicity, antiviral	Johns et al. (1983a), Sharma et al. (1992), Inada et al. (1995)
Lantadene D (**4**) (22β-isobutyroyloxy-3-oxoolean-12-en-28-oic acid)	*L. camara*, R	Leaves	?	Sharma et al. (1990)
Reduced lantadene A (**6**) (22β-angeloyloxy-3β-hydroxyolean-12-en-28-oic acid)	*L. camara*, R *L. camara*, CPR	Leaves Leaves, stem	Hepatotoxicity, antiviral	Anderson et al. (1961), Hart et al. (1976b), Seawright and Hrdlicka (1977), Inada et al. (1995)
Reduced lantadene B (**7**) (22β-dimethylacryloyloxy-3β-hydroxyolean-12-en-28-oic acid)	*L. camara*, R *L. camara*, CPR	Leaves Leaves, stem	Antiviral	Hart et al. (1976b), Inada et al. (1995)
Icterogenin (**8**) (22β-angeloyloxy-24-hydroxy-3-oxoolean-12-en-28-oic acid)	*L. camara*, TPO	Leaves, stem	Hepatotoxicity	Barton and de Mayo (1954b), Anderson et al. (1961), Brown et al. (1963), Brown (1968), Hart et al. (1976a)
Oleanonic acid (**10**) (3-oxoolean-12-en-28-oic acid)	*L. camara*, CPR *L. camara*, HW *L. camara*, CP *L. camara*, TPO *L. tiliaefolia** *L. camara** *L. indica**	Leaves, stem Roots Roots Leaves, stem Leaves, stem Leaves Roots	Inhibits leukotriene synthesis, antiinflammatory	Hart et al. (1976b), Johns et al. (1983b), Giner-Larza et al. (2001)
Oleanolic acid (**5**) (3β-hydroxyolean-12-en-28-oic acid)	*L. camara** *L. camara*, CPR *L. camara*, HW *L. camara*, CP *L. camara*, TPO *L. tiliaefolia** *L. camara** *L. indica** *L. camara**	Roots Leaves, stem Roots Roots Leaves, stem Leaves, stem Aerial parts Roots Rootlets and root bark	Antimicrobial, hepatoprotective, antiinflammatory, antihyperlipidemic, antitumour, glycogen phosphorylase inhibition	Hart et al. (1976b), John et al. (1983b), Sharma and Sharma (1989), Singh et al. (1990, 1991), Liu (1995, 2005), Siddiqui et al. (1995), Misra et al. (1997), Verma et al. (1997), Chen et al. (2005, 2006)
24-Formyl-3-oxoolean-12-en-28-oic acid (**31**)	*L. indica**	Roots	?	Singh et al. (1991)

(Continued on next page)

TABLE 3
Triterpenoids from lantana plant *(Continued)*

Compound(s)	Lantana variety	Plant part(s)	Biological activity	Reference(s)
3β,25-Epoxy-3α-hydroxy-22β-isobutanoyloxyolean-12-en-28-oic acid (**20**)	*L. cujabensis*	Stem, leaves	?	Okunade and Lewis (2004)
Ursolic acid (**26**) (3β-hydroxyurs-12-en-28-oic acid)	*L. tiliaefolia**	Leaves, stem	Antibacterial, hepatoprotective, antiinflammatory, antihyperlipidemic, antitumor, antimicrobial	Hart et al. (1976b), Johns et al. (1983b), Singh et al. (1990, 1991), Liu (1995), Verma et al. (1997)
	*L. indica**	Roots, leaves		
	*L. camara**	Roots, leaves		
Ursonic acid (**27**) (3-oxours-12-en-28-oic acid)	*L. camara*, TPO	Leaves, stem	?	Hart et al. (1976b), Johns et al. (1983b)
	*L. tiliaefolia**	Leaves, stem		
3-β,19α-Dihydroxy-ursan-28-oic acid (**29**), 21,22β-epoxy-3β-hydroxy-olean-12-en-28-oic acid (**30**)	*Lantana camara* var. *aculeata*	Roots	? ?	Misra and Laatsch (2000)
Ursethoxy acid (**28**) (3,25-epoxy-3α-ethoxy-urs-12-en-28-oic acid)	*L. camara*	Aerial parts	?	Begum et al. (2002a)
4-Epihederagonic acid (**12**) (24-hydroxy-3-oxoolean-12-en-28-oic acid)	*L. camara*, TPO	Leaves, stem	Antimicrobial	Hart et al. (1976b), Johns et al. (1983b), Verma et al. (1997)
	*L. tiliaefolia**	Leaves, stem		
	*L. camara**	Roots, leaves		
	*L. indica**	Roots, leaves		
24-Hydroxy-3-oxours-12-en-28-oic acid (**31**)	*L. tiliaefolia**	Leaves, stem	Antimicrobial	Johns et al. (1983b), Verma et al. (1997)
	*L. camara**	Roots, leaves		
	*L. indica**	Roots, leaves		
22β-Hydroxy-3-oxolean-12-en-28-oic acid (**13**)	*L. camara*, CPR	Leaves, stem	Antiviral	Hart et al. (1976b), Inada et al. (1995)
	L. camara, R	Leaves		
Lantanolic acid (**37**) (3β,25-epoxy-3α-hydroxy-olean-12-en-28-oic acid)	*L. camara**	Leaves	?	Barua et al. (1975), Sharma and Sharma (1989), Pan et al. (1993a), Barre et al. (1997), Siddiqui et al. (1995)
	*L. camara**	Leaves		
	*L. camara**	Aerial parts	?	
	*L. camara**	Roots		
Lantanone (**35**) (3β-Acetoxy-11-oxo-olean-12-en-28oic acid)	*L. camara**	Aerial parts	?	Begum et al. (2000)
Lantanilic acid (**38**) (22β-dimethylacryloyloxy-3β, 25 epoxy-3α-hydroxy-olean-12-en-28-oic acid)	*L. camara**	Leaves	?	Barua et al. (1976), Hart et al. (1976b), Siddiqui et al. (1995)
	L. camara, CP	Leaves, stem		
	*L. camara**	Aerial parts		
22β-Dimethylacryloyloxylantanolic acid (**18**)	*L. camara**	Leaves	Antimutagenic	Barre et al. (1997)
22β-Angeloyloxylantanolic acid (**19**)	*L. camara*, CP	Leaves, stem	?	Hart et al. (1976b), Barre et al. (1997)
	*L. camara**	Leaves		
Lantic acid (**14**) (3β, 25-epoxy-3α-hydroxyurs-12-en-28-oic acid)	*L. camara**	Leaves	?	Barua et al. (1969), Sharma and Sharma (1989), Barre et al. (1997), Siddiqui et al. (1995)
	L. camara, CP	Leaves, stem		
	*L. camara**	Leaves		
	*L. camara**	Aerial parts		
	*L. camara**	Roots, leaves		
	*L. indica**	Roots, leaves		
3,24-Dioxo-urs-12-en-28-oic acid (**33**)	*L. camara**	Leaves	?	Yadav and Tripathi (2003)
22β-Acetoxylantic acid (**15**)	*L. camara**	Leaves	Antibacterial	Barre et al. (1997)

TABLE 3
Triterpenoids from lantana plant *(Continued)*

Compound(s)	Lantana variety	Plant part(s)	Biological activity	Reference(s)
Betulonic acid (**42**) (3-oxolup-20(29)-en-28-oic acid)	*L. camara*, HW	Leaves, stem	?	Hart et al. (1976b)
	L. camara, CP	Leaves, stem		
Betulic acid (**43**) 3β-hydroxylup-20(29)-en-28-oic acid	*L. camara*, HW	Leaves, stem	?	Hart et al. (1976b)
	L. camara, CP	Leaves, stem		
	*L. camara**	Roots, leaves		
	*L. indica**	Roots, leaves		
Lantabetulic acid (**44**)	*L. camara*, CP	Leaves, stem	?	Hart et al. (1976b)
	*L. camara**	Roots, leaves		
	*L. indica**	Roots, leaves		
Camarilic acid (**21**) (3,25-epoxy-3α-methoxy-22β-[(Z)-2′methyl-2′-butenyloxy]-12-oleanen-28-oic acid)	*L. camara**	Aerial parts	?	Begum et al. (1995)
Camaracinic acid (**22**) (3,25-epoxy-3α-methoxy-22β-[(Z)-2′methyl-2′-butenyloxy]-12-ursen-28-oic acid)	*L. camara**	Aerial parts	?	Begum et al. (1995)
Camarinic acid (**17**) (22β-acetoxy-3,25-epoxy-3α-hydroxy-12-ursen-28-oic acid)	*L. camara**	Aerial parts	Nematicidal	Siddiqui et al. (1995), Begum et al. (2000)
Camaric acid (**16**) (3,25-epoxy-3α-hydroxy-22β [2-methyl-2Z-butenoyloxy]-12-oleanen-28-oic acid)	*L. camara**	Aerial parts	?	Siddiqui et al. (1995), Misra et al. (1997)
	*L. camara**	Rootlets, root, bark		
Camaryolic acid (**39**) (3,25-epoxy-3α-methoxy-22β-[β,β-dimethylacryloyloxy] urs-12-en-28-oic acid)	*L. camara**	Aerial parts	?	Begum et al. (2003)
Methyl camaralate (**40**) (22β-acetoxy-3,25-epoxy-3α-hydroxy-yurs-12-en-28-oic acid)			?	
Camangeloyl acid (**41**) (3,25-epoxy-3α-hydroxy-22β-[(Z)-2′methyl-2′-butenoyloxy]-11-oxoolean-12-en-28-oic acid)		?		
Pomolic acid (**45**)	*L. camara* (Yellow flower)	Stem	?	Huang and Huang (2004)
Ursoxy acid (**23**) (3,25-epoxy-3α-methoxy-urs-12-en-28-oic acid)	*L. camara*	Aerial parts	?	Begum et al. (2002b)
Methyl Ursoxylate (**24**) (Methyl 3,25-epoxy-3α-methoxy-urs-12-en-28-oic acid)Ursangillic acid (**25**) (3,25-epoxy-3α-ethoxy-22β-[(Z)-2′-methylbut-2-enyloxy]urs-12-en-28-oic acid)				

(Continued on next page)

TABLE 3
Triterpenoids from lantana plant *(Continued)*

Compound(s)	Lantana variety	Plant part(s)	Biological activity	Reference(s)
Camarolide (**11**) (3-keto-urs-11-en-13β(28)-olide)	*L. camara*	Aerial parts	?	Siddiqui et al. (2000)
Lancamaric acid (**36**) (3,25-epoxy-3α-ethoxy-olean-12-en-28-oic acid)				
25-Hydroxy-3-oxoolean-12-en-28-oic acid (**32**)	*L. camara*	Roots	?	Singh et al. (1996)
3β, 24-Dihydroxyolean-12-en-28-oic acid (**9**)	*L. indica*	Roots	?	Singh et al. (1990)
5,5-Trans-fused cyclic lactone-containing euphane triterpenoids (**46**)	*L. camara**	Leaves	Antithrombin	O'Neill et al. (1998), Weir et al. (1998)

Note. R, Red variety of *L. camara* present in the temperate parts of India; TPO, Townsville prickly orange; CPR, Common pink-edged red; SR, Southern red; HW, Helidon white; BR, Brick red; TRP, Townsville red-centered pink; LO, Large flowered orange; MRP, Mackay red-centered pink; CP, Common pink; *, Variety not mentioned by authors.

in previous investigations of lantadene fractions, was reported from some taxa of *L. camara* and was characterized as 22β-[(*S*)-2-methylbutanoyloxy]-3-oxoolean-12-en-28-oic acid (**3**), and is presently known as LC (**3**) (Figure 1) (Sharma et al., 1992). LC was also prepared in two polymorphic forms, but unlike LA both the crystalline (form I) and amorphous (form II) forms of LC elicited strong hepatotoxic response in guinea pigs (Sharma et al., 1992). Another related triterpenoid, icterogenin (Figure 1), reported from only the Townsville prickly orange variety of *L. camara,* is also a potent hepatotoxin (Anderson et al., 1961; Brown, 1968). Icterogenin was reported to inhibit biliary excretion in rabbits (Heikel et al., 1960). The biological activity of LD has not been investigated. The phototoxic phytochemicals, namely, porphyrins in *L. camara* have also been reported to cause toxicity in grazing sheep and goats (Towers, 1984).

Molecular Structure of Lantadenes

Molecular structures of LA (**1**), LB (**2**), LC (**3**), RLA (**6**), and RLB (**7**) have been determined (Pattabhi et al., 1991; Netha Ji et al., 1993; Kabaleeswaran et al., 1996). The substitution at the 22 position is β-axial. The rings A, B, C, D, and E (Figure 1) are *trans*, *trans*, *trans*, and *cis* fused, forming an extended structure in all the molecules. LA, LB, and LC are similar except for the side chain (at C22); atoms C32 and C33 are connected by a single bond in LC and double bond in LA (Figure 1). Hence, the side chain conformation in LA and LB is identical with that of LC (Pattabhi et al., 1991; Netha Ji et al., 1993). The differences observed in the side chain conformation of LA, LB, and LC are due to the presence or absence of double bond at C32. LC has an asymmetric carbon at C32 (Figure 1). This has been lost in lantadene A and B due to the presence of the double bond. The differences in side chain conformation suggest that LC might be binding to a receptor for its bioactivity, where the asymmetric carbon and carbonyl oxygen (O5) have an important role to play. Further, the presence of two methyl groups at C33 in LB (Figure 1) may be posing steric hindrance to the active site of receptor for hepatotoxicity. One is tempted to speculate that the C34 atom in LA (form I), which is in *cis* conformation with respect to C31, may rotate to the *trans* position in form II as in the case of LC, which makes it hepatotoxic. However, the potency of LA (form II) and LC may differ due to the presence of an asymmetric carbon atom at C32 in LA (Sharma et al., 1991a, 1992; Pattabhi et al., 1991; Netha Ji et al., 1993).

IV. TOXICOSIS

The lantana menace to livestock is two-pronged: hepatotoxicity and photosensitization in grazing animals, and allelopathic action on grasses and other vegetation in the pastures, causing fodder scarcity (Sharma et al., 1988b). Records of field cases of lantana poisoning are summarized in Table 6. The incidence of lantana poisoning varies from sporadic cases throughout the year to heavy outbreaks during drought or flood conditions when fodder is scarce (Yadava and Verma, 1978; Sharma and Makkar, 1981). Incidence of lantana poisoning has also been reported during transportation of animals from lantana-free regions to lantana-infested areas (Sharma et al., 1981b; Tokarnia et al., 1984) or on leaving the animals for grazing in lantana-infested localities after some period of stall feeding (Sharma et al.,1988b).

Immediately after eating lantana foliage, the animals suffer from constipation and stop feeding in about 2 h. In the next 24–48 h the animals become sedated and photosensitive. Subsequently, eyelids, muzzle, and other hairless parts become swollen (Yadava and Verma, 1978; Sharma et al., 1981b). The course of illness and severity of symptoms depend upon the quantity of foliage eaten (Sharma et al., 1988b). With regard to

TABLE 4
Other natural products from lantana plant

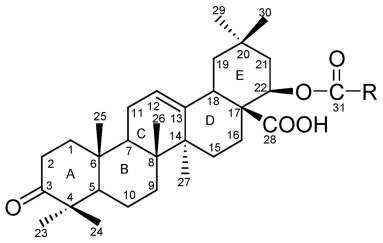
Compound(s)	Lantana spp.	Plant part(s)	Biological activity	Reference(s)
Flavonoids				
Umuhengerin (**47**) (5-hydroxy-6,7,3′,4′,5′-pentamethoxyflavone)	*L. trifolia*	Leaves	Antibacterial	Rwangabo et al. (1988)
Camaraside (**48**) (3,5-dihydroxy-4′,6-dimethoxyflavanol-7-O-glucopyranoside)	*L. camara*	Leaves	Antitumour	Mahato et al. (1994)
Penduletin (**49**) Chrysorplenetin (**50**)	*L. achyranthifolia*	Aerial parts	?	Dominguez et al. (1983)
Linaroside (**51**) (7-O-(β-D-glucopyranosyl)-6,4′-dimethoxy-5-hydroxy flavone)	*L. camara*	Aerial parts	Nematicidal	Begum et al. (2000)
Lantanoside (**52**) (7-O-(6′′-O-acetyl-β-D-glucopyranosyl)-6,4′-dimethoxy-5-hydroxy flavone)	*L. camara*	Aerial parts	Nematicidal	Begum et al. (2000)
Camaroside (**53**) (4′,5-dihydroxy-3,7-dimethoxy flavone-4′-O-β-D-glucopyranoside)	*L. camara*	Leaves	?	Pan et al. (1993b)
3-methoxy quercertin (**54**) 3,7-dimethyl quercertin (**55**) 3,7,4′-trimethoxy quercertin (**56**)	*L. camara* *L. montevidensis*	Leaf exudates	?	Wollenweber et al. (1997)
Apigenin (**57**) Cirsilineol (**58**) Cirsiliol (**59**) Eupafolin (**60**) Eupatorin (**61**) Hispidulin (**62**)	*L. montevidensis*	Leaves	Antiproliferative	Nagao et al. (2002)
Iridoid Glycosides				
Theveside (**63**) Theviridoside (**64**) Geniposide (**65**) 8-Epiloganin (**66**) Shanzhsid methyl ester (**67**) Lamiridoside (**68**)	*L. camara*	Roots	?	Pan et al. (1992)
Oligosaccharides				
Ajugose (**69**) Stachyose (**70**) Verbascotetracose (**71**) Verbascose (**72**) Lantanose A (**73**) Lantanose B (**74**)	*L. camara*	Roots	?	Pan et al. (1992)
Phenylproponaoid glycosides				

(Continued on next page)

TABLE 4
Other natural products from lantana plant *(Continued)*

Compound(s)	Lantana spp.	Plant part(s)	Biological activity	Reference(s)
Verbascoside (**75**)	*L. camara*	Leaves	Inhibition of protein kinase C, antitumor	Herbert et al. (1991)
Martynoside (**76**)	*L. camara*	Leaves, branchlet	Cardioactive	Syah et al. (1998)
Lanatanaside (**77**)	*L. camara*	Leaves	Antitumour	Mahato et al. (1994)
Naphthoquinones				
Furano-1,4-naphthoquinone (**78**)	*L. achyranthifolia*	Roots	?	Dominguez et al. (1983)
5-Hydroxynaphtho [2,3-β] furan-4,9-quinone (**79**)	*L. camara,*	Roots	?	Abeygunawardena et al. (1991)
8-Hydroxynaphtho [2,3-β] furan-4,9-quinone (**80**)	*L. achyranthifolia*			
6-Methoxynaphtho [2,3-β] furan-4,9-quinones (**81**)				
7-Methoxynaphtho [2,3-β] furan-4,9-quinones (**82**)				
Lantalucratins A-F (**83–88**)	*L. involucrata*	Roots	Antitumor	Hayashi et al. (2004)
Essential oil constituents				
β-cymene, α-phellandrene, α-pinene, dipentene, γ-terpinene, caryophyllene, cadinene, cineol, linalool,	*L. camara*	Leaves	?	Dutt (1950), Sharma and Sharma (1989)
(E)-Caryophyllene, γ-cadinene, α-pinene, ocimene germacrene	*L. xenica*	Aerial parts	Antibacterial	Juliani et al. (2002)
α-phellandrene, dipentene, α-terpineol, geraniol, cineol, eugenol, citral, furfural, phellandrone, linalool	*L. camara*	Leaves, flowers and stem	?	Ahmed et al. (1972)
Citral	*L. camara* var. *aculeata*, *hybrida, flava, nivea*, *mista*	-	?	Saleh (1974)
α-farnesene, α-phellandrene, Longifolene, α-cedrene, β-caryophyllene	*L. camara*	Leaves	?	Gurdip et al. (1991)
Carvacrol, 1,8-cineole, isocaryophyllene, β-bisabolene and α-bisabolol	*L. achyranthifolia*	Aerial parts	Antibacterial	Hernandez et al. (2005)
Allelochemicals				
Umbelliferone (7-hydroxycoumarin) 6-methylcoumarin, salicylic acid gentisic acid, β-resorcylic acid α-resorcylic acid, p-hydroxybenzoic acid vanillic acid, caffeic acid, p-coumaric acid vanillin, ferulic acid, quercetin	*L. camara*	Leaves	Allelopathy (phytotoxicity)	Singh et al. (1989)

Triterpenoids

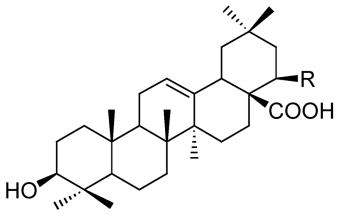


(1) R = -C(CH$_3$) =CH(CH$_3$)
Lantadene A

(2) R = -CH=C(CH$_3$)$_2$
Lantadene B

(3) R = -CH(CH$_3$)CH$_2$CH$_3$
Lantadene C

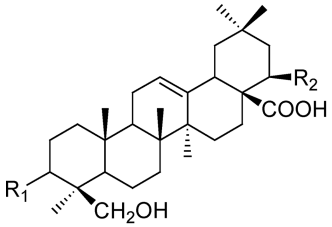
(4) R = -CH(CH$_3$)$_2$
Lantadene D



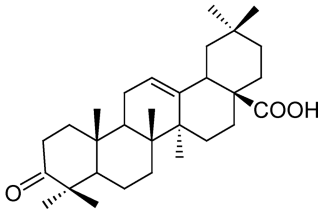
(5) R = H
Oleanolic acid

(6) R = -OCOC(CH$_3$) =CH(CH$_3$)
Reduced Lantadene A

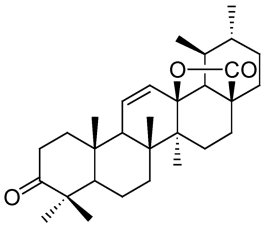
(7) R = -OCO-CH=C(CH$_3$)$_2$
Reduced Lantadene B



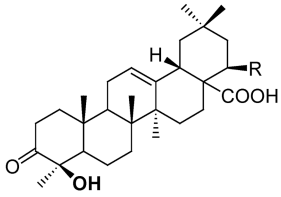
(8) R$_1$ = O; R$_2$ = -OCOC(CH$_3$) =CH(CH$_3$)
Icterogenin
(9) **R**$_1$ = OH; R$_2$ = H
3ß,24-dihydroxyolean-12-en-28-oic acid



(10) Oleanonic acid

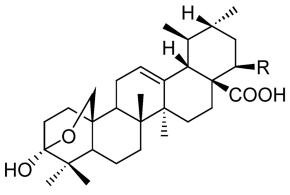


(11) Camarolide



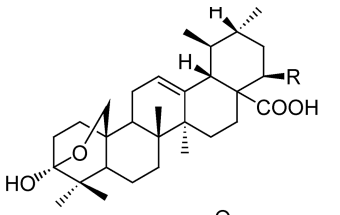
(12) R = H
4- Epihederagonic acid

(13) R = OH
22ß-hydroxy-3-oxolean-12en-28-oic acid

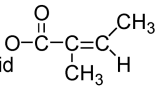


(14) R = H
Lantic acid
(15) R = -OCOCH$_3$
22ß- acetoxylantic acid

FIG. 1. Chemical structures of triterpenoids, flavonoids and other natural products of Lantana plant. *(Continued)*

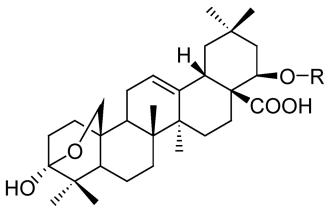


(16) R = Camaric acid



(17) R = -$OCOCH_3$

Camarinic acid

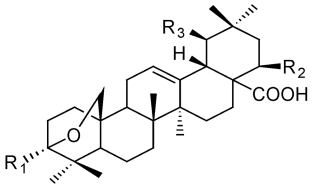


(18) R = -$COCH=C(CH_3)_2$

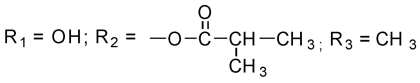
22ß-Dimethylacryloyloxy lantanolic acid

(19) R = -$COC(CH_3)=CH(CH_3)$

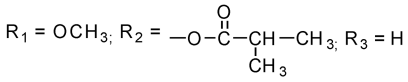
22ß- Angeloxylantanolic acid

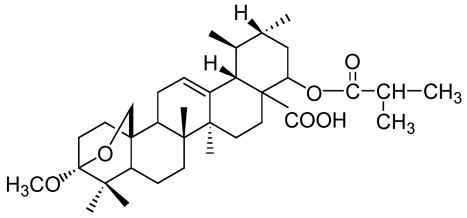


(20) 3ß-25-epoxy-3a-hydroxy-22ß-isobutanoyloxyolean-12-en-28-oic acid

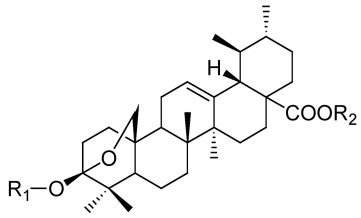


(21) Camarilic acid

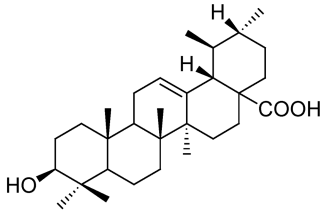




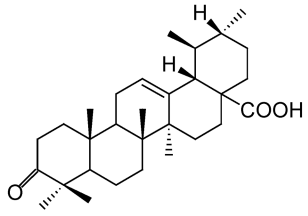
(22) Camaracinic acid



(23)	R_1 R_2
Ursoxy acid	CH_3 H
(24)	R_1 R_2
Methyl Ursoxylate	CH_3 CH_3
(25)	
Ursangillic acid	C_2H_5 $-C(CH_3)=CH$

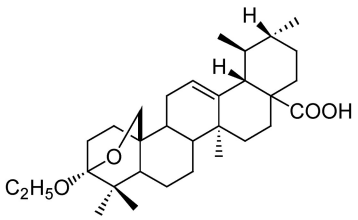


(26) Ursolic acid

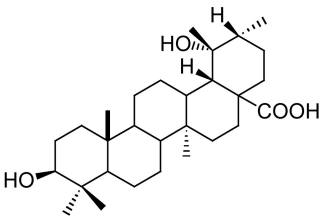


(27) Ursonic acid

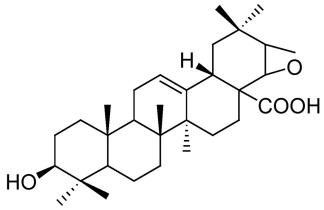
FIG. 1. (*Continued*)



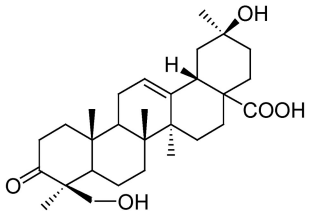
(28) Ursethoxy acid



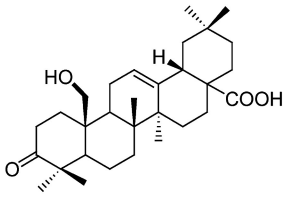
(29) 3-β,19α-Dihydroxy-ursan-28-oic acid



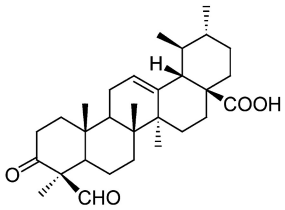
(30) 21,22-Epoxy-3β-hydroxy-olean-28-oic acid



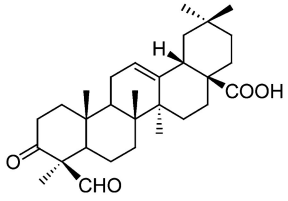
(31) 24-hydroxy-3-oxours-12-ene-28-oic acid



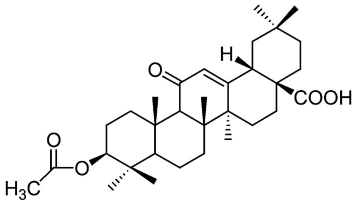
(32) 25-hydroxy-3-oxoolean-12-ene-28-oic acid



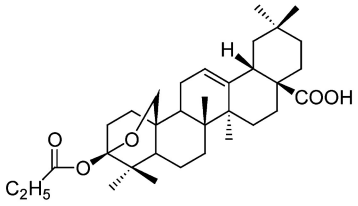
(33) 3,24-dioxo-urs-12-en-28-oic acid



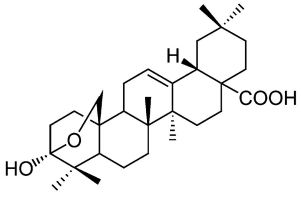
(34) 24-Fromyl-3-oxolean-12-en-28-oic acid



(35) Lantanone

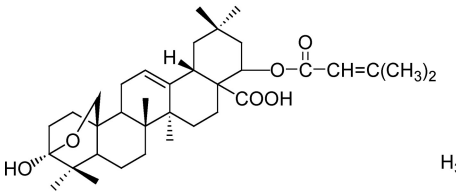


(36) Lancamaric acid

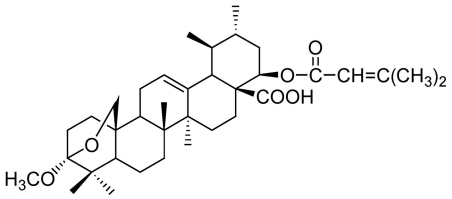


(37) Lantanolic acid

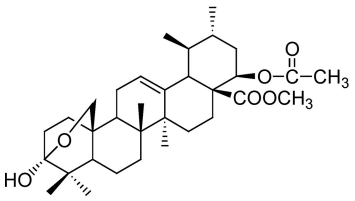
FIG. 1. (*Continued*)



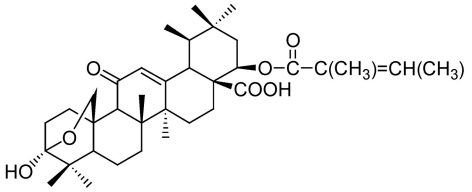
(38) Lantanilic acid



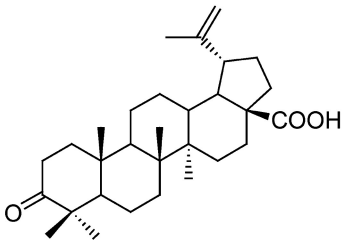
(39) Camaryolic acid



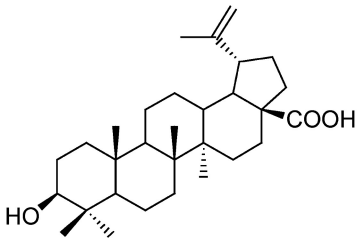
(40) Methyl camaralate



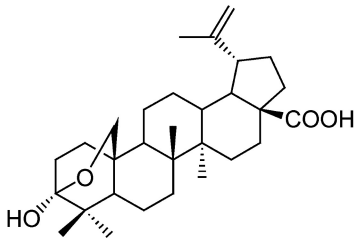
(41) Camangeloyl acid



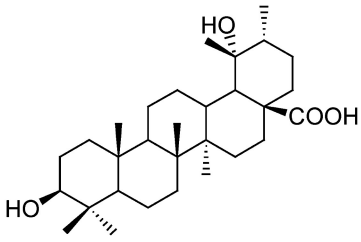
(42) Betulonic acid



(43) Betulic acid

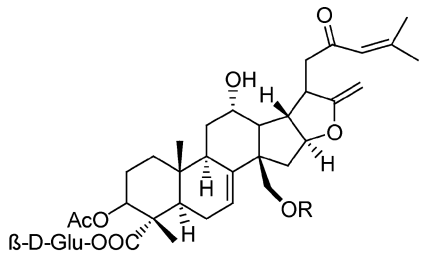


(44) Lantabetulic acid

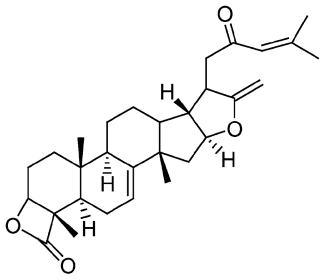


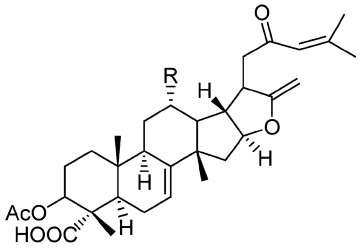
(45) Pomolic acid

FIG. 1. (*Continued*)



R1 = H
R2 = Ac

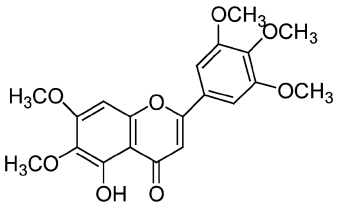




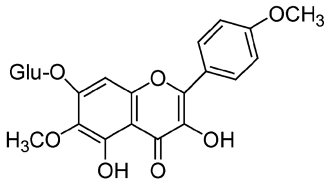
R1 = H
R2 = OH

(46) 5,5- trans fused cyclic lactone containing euphane triterpenoids

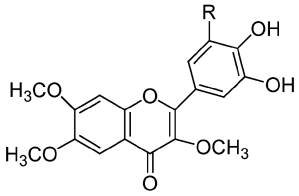
Flavanoids



(47) Umuhengerin

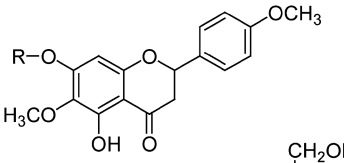


(48) Camaraside

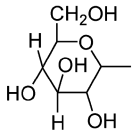


(49) R = H
Penduletin

(50) R = OCH_3
Chrysosplenetin

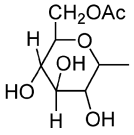


(51) R =



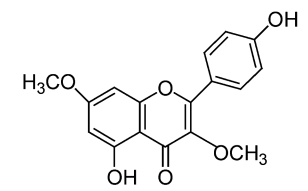
Linaroside

(52) R =

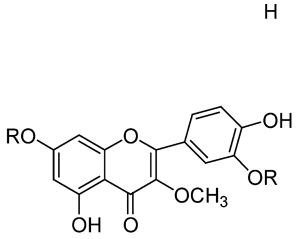


Lantanoside

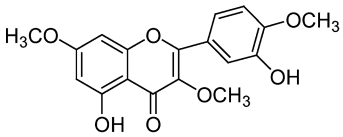
FIG. 1. (*Continued*)



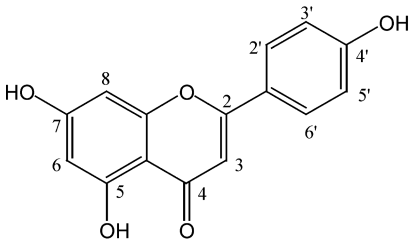
(53) Camaroside



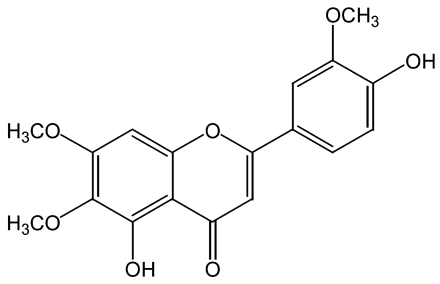
(54) 3-methoxy quercertin
R = H
(55) 3,7-dimethoxy quercertin
R = CH_3



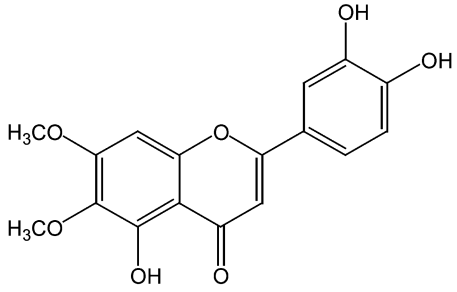
(56) 3,7,4'-trimethoxy quercertin



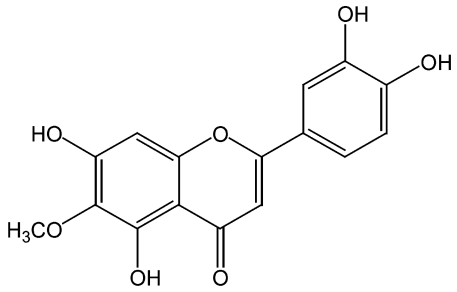
(57) Apigenin



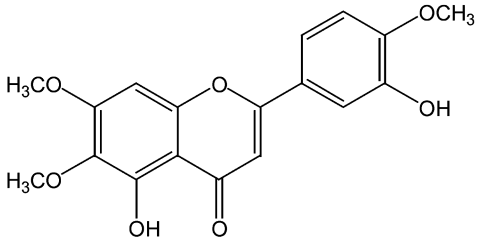
(58) Cirsilineol



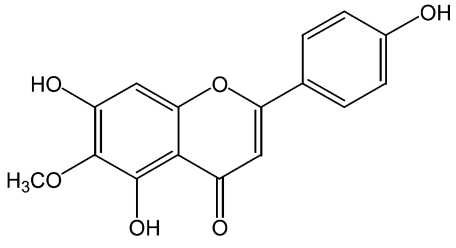
(59) Cirsiliol



(60) Eupafolin



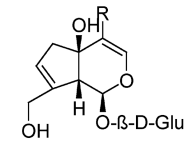
(61) Eupatorin



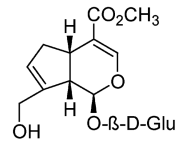
(62) Hispidulin

FIG. 1. (*Continued*)

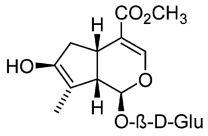
Iridoid Glycosides



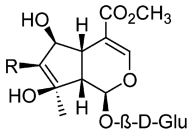
(63) Theveside
R = $CO_2^-Na^+$
(64) Theviridoside
R = CO_2CH_3



(65) Geniposide

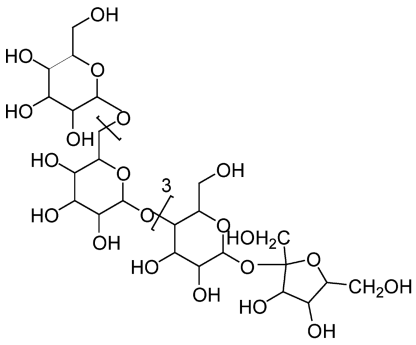


(66) 8- Epiloganin

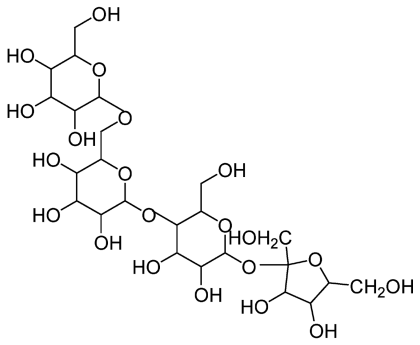


(67) Shanzhside methyl ester
R = H
(68) Lamiridoside
R = OH

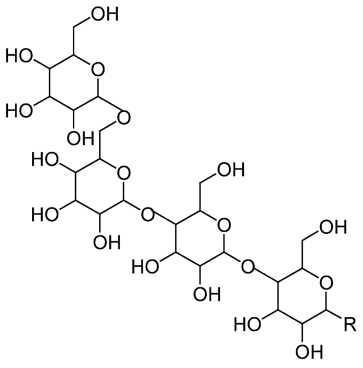
Oligosaccharides



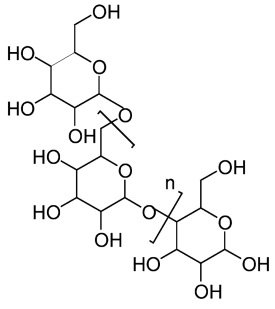
(69) Ajugose



(70) Stachyose



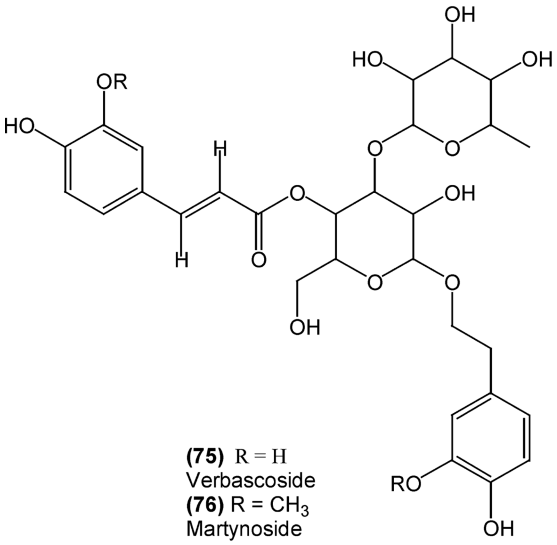
(71) Verbascotetracose
R = OH
(72) Verbascose
R = a-(ß-fructofuranosyl)



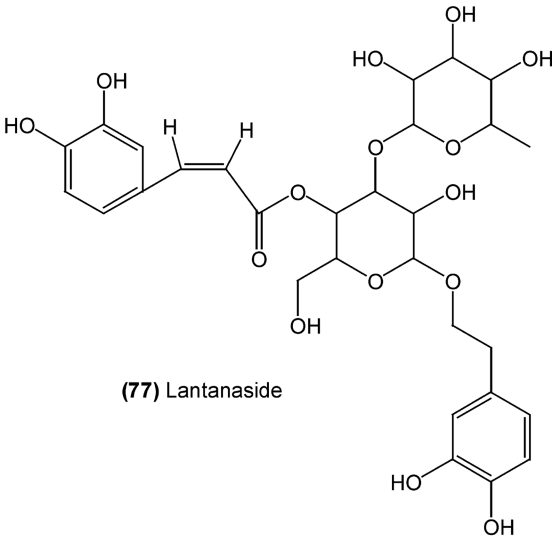
(73) Lantanose A
n = 3
(74) Lantanose B
n = 4

FIG. 1. (*Continued*)

Phenylpropanoid Glycosides

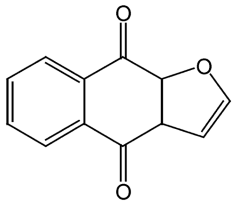


(75) R = H
Verbascoside
(76) R = CH_3
Martynoside

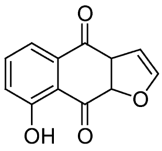


(77) Lantanaside

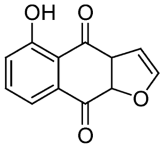
Naphthoquinones



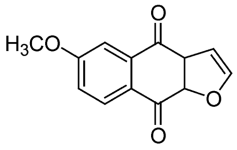
(78) Furano-1,4-naphthoquinone



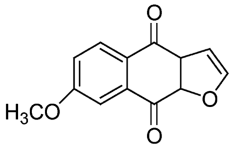
(79) 5-Hydroxy naptho[2,3-β]furan-4,9 quinone



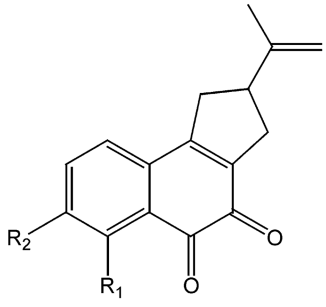
(80) 8-Hydroxy naptho[2,3-β]furan-4,9 quinone



(81) 6-Methoxynaptho[2,3-β]furan-4,9 quinone

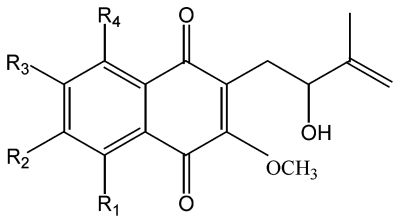


(82) 7-Methoxynaptho[2,3-β]furan-4,9 quinone



Lantalucratin A **(83)** $R_1 = OCH_3$ $R_2 = H$
B **(84)** $R_1 = OH$ $R_2 = H$
C **(85)** $R_1 = H$ $R_2 = H$

FIG. 1. (*Continued*).



Lantalucratin D **(86)** $R_1 = OCH_3$ $R_2 = H$ $R_3 = H$ $R_4 = H$
E **(87)** $R_1 = OCH_3$ $R_2 = H$ $R_3 = H$ $R_4 = OH$
F **(88)** $R_1 = H$ $R_2 = OCH_3$ $R_3 = OH$ $R_4 = OH$

FIG. 1. (Continued)

species vulnerability, lantana poisoning has been demonstrated in cattle, buffaloes, sheep, and goats (Table 6) (Sharma et al., 1988b; Sharma and Makkar, 1981). Lal and Kalra (1960) observed goats to be less vulnerable than other animals. There appear to be some inherent, hitherto uncharacterized metabolic factors in goats that enable them to withstand, at least to some extent, the lantana scourge (Sharma et al., 1988b). Native goats from Taiwan were found tolerant to *L. camara* poisoning, in addition to finding the plant unpalatable (Lin et al., 1985). Horses and male rats were reported not to be susceptible to lantana poisoning (Pass, 1991). Later, lantana toxicity in horses was also reported (Morton, 1994). Resistance in male rats has been attributed to the presence of testosterone (Pass et al., 1979a, 1985). Neonatal lambs and calves also appear to be resistant to poisoning by LA (**1**) (Pass, 1991). No difference has been found in the incidence of lantana poisoning among different breeds of cattle, but parasitic infestation may be a predisposing factor (Frisch et al., 1984). In a survey of the Kangra valley of Himachal Pradesh in India, Sharma and Makkar (1981) observed lantana poisoning as the main cause for loss of livestock. The incidence was maximum during summer months April–June, before the onset of rainy season, when there is a scarcity of green forage (Sharma and Makkar, 1981; Sharma, 1994).

The effect of a hydroalcoholic extract of the leaves of *L. camara* var. *aculeata* was investigated in male rats by de Mello and coworkers (2003). The extract did not interfere with the overall weight or internal organ weights but interfered with sperm count, daily sperm production, and sperm morphology in a dose-dependent manner (de Mello et al., 2003). The administration of hydroalcololic extract to female rats caused fetal abnormalities, embryotoxicity, and implantation losses (Mello et al., 2005).

A. Mechanism of Lantana Toxicity

1. Toxin Uptake From Gastrointestinal Tract

When lantana leaf powder was given into different regions of the alimentary tract of adult merino ewes, absorption sufficient to cause toxicity occurred from stomachs, small intestine, and large intestine. The absorption from the small intestine was quantitatively most important. It was observed that the passage of ingesta into the small intestine decreased markedly a few hours after the lantana leaf powder was administered (Pass et al., 1981a). The absorption of the toxin from all regions of the gastrointestinal tract (GIT) is important for the progression of toxicity. When bile was diverted from the small intestine, the animals were still intoxicated. Thus, bile is not important for the absorption of lantana toxins. After absorption, the toxins are transported to the liver in portal blood, since drainage of lymph in sheep did not prevent intoxication (Pass et al., 1981a). There is marked difference in the oral (60 mg/kg) and intravenous dose (1–3 mg/kg) of LA (**1**), which caused cholestasis and hepatotoxicity in sheep (Seawright and Hrdlicka, 1977; Pass et al., 1979b). An intravenous dose greater than 3 mg/kg induced hepatic necrosis rather than typical cholestatic lesions of lantana poisoning (Pass et al., 1979b). A comparison of the studies of Seawright and Hrdlicka (1977) and Pass et al. (1979b) implied that no biotransformation of LA (**1**) in the GIT is necessary for its hepatotoxic action. A single intravenous dose of LA induces only mild cholestasis, but if the dose is given twice daily for several days, typical cholestasis of lantana poisoning occurs (Pass, 1991). Continuous absorption of the toxin is required for the disease to be maintained over a long period of time (Pass, 1991). Also, rumen contents in lantana-poisoned animals become more toxic with time, possibly due to slow release of the toxins from the leaf sample ingested, and if the contents are emptied the animals show rapid recovery (McSweeney and Pass, 1982). Ruminal stasis is another important feature of lantana poisoning (Table 5). The onset of ruminal stasis is associated with a decrease in the flow of stomach contents into the duodenum (Pass et al.m 1981a). The development of ruminal stasis causes large amounts of the toxins to be retained in it, and if transferred to the rumen of a normal animal, lantana poisoning occurs (McSweeney and Pass, 1982). Direct action of the triterpene acids on the intestinal muscles, as determined under in vitro conditions, was initially incriminated in the paralysis of intestinal muscle (Rimington et al., 1937). However, paralysis of the intestinal muscles under in vivo conditions was later ruled out (Pass and Heath, 1978). The stasis of rumen in lantana intoxicated animals is due, initially, to inhibitory neural impulses arising from damaged liver and to the effect of anorexia (McSweeney and Pass, 1983b). Ruminal stasis occurs 4–6 h after ingestion of lantana,

TABLE 5
Experimental lantana toxicity in different animal species

Application	Animal species	Observations	Reference
Lantanin (subsequently named lantadene A) (2 g administered orally)	Sheep	Severe icterus and photosensitization similar to that of lantana lead powder administered	Louw (1943)
Lantadene B (4 g in two divided doses of 2 g each)	Sheep	Nontoxic	Louw (1948)
Leaf powder of *L. camara* (4 and 8 g/kg body weight)	Sheep	Mild photosensitization, conjunctivitis, excoriation of hairless skin of muzzle, liver was bile stained, acute cholecystitis was occasionally found	Seawright (1963a)
Leaf powder of *L. camara* (6, 12 g/kg body weight)	Sheep	Jaundice and photosensitization, necrosis of liver, kidneys and pulmonary edema	Seawright (1964)
Leaf powder of *L. camara* (4 g/kg body weight)	Cattle	Depression, anorexia, constipation within 24 h of dosing, jaundice of sclera and visible mucous membranes, the liver was swollen mottled and pale yellow, kidneys were swollen and moist at the cut surface	Seawright and Allen (1972)
Leaf powder of *L. camara*, orally suspended in water.	Sheep		Gopinath and Ford (1969)
Group I: 10 g/kg body weight (as single dose)		Anorexia by day 2 and icteric by day 4, swelling of face, eyelids and ears by day 7. The icterus regressed by day 10, the swelling reduced and ears became scabby	
Group II: 5 g/kg body weight (on two consecutive days)		Anorexic and icteric by day 2-3. Swelling of the ears and face as in group I animals. By day 5 the swollen ears and eyelids commenced to exude serum and the sheep were very depressed	
Group III: 2 g/kg (on five consecutive days)		Showed slight anorexia from day 3-6 but rapidly regained their appetite when dosing ceased	
Leaf powder of *L. camara*	Goats		Obwolo et al. (1990)
Group I. 5 g/kg body weight once		Diarrhea, depression, anorexia, dehydration, jaundice and ruminal stasis developed in all the animals. No evidence of photosensitization in any animal	
Group II: 10 mg/kg body weight initially followed by 5 g/kg body weight weekly for 4 weeks		Necropsy observations were ruminal impaction, pulmonary edema, hepatocyte cytoplasmic vacuolation and necrosis as well as mild renal tubular necrosis.	
Leaf powder of *L. camara*, orally suspended in water at the dose of 125 g and 250 g per animal (body weight 50–70 kg) for four days.	Buffaloes	Severe constipation, dysenteric stools, inappetance, jaundice, catarrhal conjunctivitis, suppression of ruminal motility, symptoms appeared earlier in animals receiving higher dose	Dhillon et al. (1970), Dhillon and Paul (1971)

TABLE 5
Experimental lantana toxicity in different animal species *(Continued)*

Application	Animal species	Observations	Reference
Aqueous extract of *L. camara* leaves (Extracted 250 g of the leaf powder in Soxhlet apparatus for dosing each animal (body weight 50–70 kg). Repeated the dose on four days	Buffaloes	Nontoxic	Dhillon et al. (1970)
Leaf powder of *L. camara* (6 g/kg body weight)	Guinea pigs	Sedated within 48–72 h of dosing, jaundice and photosensitization, moribund in 4–7 days, liver had yellowish patches and was swollen, kidneys were yellowish brown and much larger in size, epidermis was yellow presumably due to bilirubin deposition, stomach was filled with gas, the gall bladder was shrunken, urinary bladder was full of urine, marked increase in serum bilirubin content	Sharma et al. (1980)
Leaf powder of *L. camara* (6 g/kg body weight) and partially purified toxins from *L. camara* leaves (125 mg/kg body weight)	Rabbits	Anorexia, decrease in fecal output, and ictericity, marked increase in the size of kidneys, liver was fragile and ochre colored	Sharma et al. (1988c)
Lantadene A, orally in gelatin capsules (167 mg/kg body weight)	Lamb	Nontoxic	Seawright (1965a)
Lantadene A, orally in gelatin capsules (667 mg/kg body weight)	Guinea pig	Nontoxic	Seawright (1965a)
Black tarry extract obtained during chromatography of the extract of *L. camara* leaves, orally in gelatin capsules (500 mg/kg body weight)	Lamb	Anorexia, jaundice, photosensitization and death 18 days after dosing	Seawright (1965a)
Black tarry extract obtained during chromatography of the extract of *L. camara* leaves, orally in gelatin capsules (1.17 to 5.8 g/kg body weight)	Guinea pigs	Anorexia, constipation, jaundice, urine samples collected on third day after dosing positive for bile pigment, distension of the stomach and duodenum with gas from fermenting food in the stomach, liver was pale, swollen and mottled	Seawright (1965a)
Lantadene A, dissolved in 96% ethanol and diluted with 0.1 N sodium hydroxide and normal saline. Intravenous injection (1 to 8 mg/kg body weight)	Sheep	A single dose of 1-3 mg/kg caused mild hepatocellular injury with transient rise in serum enzymes with or without hyperbilirubinaemia. Higher doses induced cholestasis and hepatic necrosis.	Pass et al. (1979b)
Lantadene A, orally in gelatin capsules (65 mg/kg body weight) and lantadene A, dissolved in DMSO, intraruminally (75 mg/kg body weight)	Sheep	Anorexia, constipation, jaundice, photosensitization, livers were swollen and ochre colored, kidneys were swollen, with each cortex pale, yellowish and moist	Seawright and Hrdlicka (1977)

(Continued on next page)

TABLE 5
Experimental lantana toxicity in different animal species *(Continued)*

Application	Animal species	Observations	Reference
Reduced lantadene A	Sheep		Seawright and Hrdlicka (1977)
Orally in gelatin capsules (80 mg/kg body weight)		Nontoxic	
Intraruminally, dissolved in DMSO (42, 80 mg/kg body weight)		Anorexia, constipation, jaundice, photosensitization, livers were swollen and ochre colored, kidneys were swollen, with each cortex pale, yellowish and moist	
Lantadene B	Sheep		Seawright and Hrdlicka (1977)
Orally in gelatin capsules (300 mg/kg body weight)		Nontoxic	
Intraruminally, dissolved in DMSO (200, 240, 250, 300 mg/kg body weight)		Anorexia, constipation, jaundice, photosensitization, livers were swollen and ochre colored, kidneys were swollen, with each cortex pale, yellowish and moist	
Reduced lantadene A dissolved in olive oil, orally (ED50, 15 mg/kg body weight)	Female rats	Animals depressed the day after dosing, hair coat erect and unkempt, vaginal mucous membrane yellow, decrease in feed intake, bilirubin detected in urine the day after dosing.	Pass et al. (1979a)
Partially purified toxins of *L. camara* leaves, orally in gelatin capsules (125 mg/kg body weight)	Guinea pigs	Sedated, icteric and photosensitive at 24-48 after dosing, increase in plasma bilirubin levels	Sharma et al. (1987)
Lantadene A, orally in gelatin capsules (1.2 g/kg body weight)		Nontoxic	Sharma et al. (1987)
Partially purified toxins of *L. camara* leaves, administered orally filled in gelatin capsules:	Guinea pigs		Sharma et al. (1988a)
Form I (crystalline), 125 mg/kg body weight		Nontoxic	
Form II (amorphous) 125 mg/kg body weight		Anorexia and constipation, Icteric within 24 h of dosing, severely icteric, photosensitive and moribund by third day, hepatomegaly (nearly 55% increase in liver size), gall bladder contents looked very dark, opaque and viscous	
Partially purified toxins of *L. camara* leaves, orally, to both male and female guinea pigs (125 mg/kg body weight)	Guinea pigs	Hepatotoxicity in both male and female guinea pigs. Anorexia, decrease in fecal output, ictericity and photosensitization within 48 h after dosing. Hepatomegaly in all the animals in test groups	Sharma et al. (1989)
Lantadene A (22–170 mg/kg body weight), intraperitoneally	Rabbits	Cholestasis	Heikel et al. (1960)

TABLE 5
Experimental lantana toxicity in different animal species *(Continued)*

Application	Animal species	Observations	Reference
Lantadene B (50 mg, 100 mg/kg body weight), intraperitoneally	Rabbits	Nontoxic	Brown and Rimington (1963)
Lantadene A (50, 80, 100 mg/kg body weight), intraperitoneally	Rabbits	Nontoxic	Brown et al. (1963)
Lantadene A Form I (crystalline) orally in gelatin capsules (125 mg/kg body weight)	Guinea pigs	Nontoxic	Sharma et al. (1991a)
Form II (amorphous) orally in gelatin capsules (125 mg/kg body weight)		Marked decrease in feed in take and fecal output within 24 h after dosing, icteric, photosensitive and moribund in 24–48 h after dosing, severity of ictericity increased with time, marked increase in level of conjugated form of bilirubin in blood plasma	
Lantadene C, form I (crystalline) and form II (amorphous) both orally in gelatin capsules (125 mg/kg body weight)	Guinea pigs	Both form I and II of lantadene C caused marked decrease in feed in take and fecal output within 24 h after dosing. Severely icteric, photosensitive and moribund in 24-48 h. Marked increase in level of conjugated form of bilirubin in blood plasma. On necropsy the subcutaneous layer was found to be deep yellow, the stomach was empty and filled with gas, the large intestines contained shrunken feces, the liver was markedly enlarged, mottled and brownish yellow, the kidneys and lungs also had yellow coloration; the gall bladder was shrunken, looked very dark and opaque and its contents were very viscous, dark brown and opaque. In contrast the gall bladder contents of control animals were watery in consistency and greenish yellow in color.	Sharma et al. (1992)
Hydroalcoholic extract of *L. camara* var. aculeata leaves (1, 3, 7 g/kg body weight)	Rats	Fetal abnormalities, embryotoxicity with postimplantation losses	Mello et al. (2005)

DMSO, dimethyl sulfoxide.

which is approximately the time when liver injury is first evident (Pass et al., 1978a; McSweeney and Pass, 1983b). Copious amounts of fluid in the stomach and intestines, dry rumen contents, and a large dry bolus-like accumulation in proximal colon were thought to be due to paralysis of musculature of the GIT leading to intestinal stasis (Seawright, 1963). However, based on recordings of pressure changes in the duodenum, jejunum, cecum, and spiral colon of the affected sheep, it was reported that lantana poisoning did not cause intestinal paralysis (Pass and Heath, 1978).

TABLE 6
Toxicosis of lantana plant in different regions of the world

Plant	Place/Country	Animals affected	Symptoms and effects	References
L. camara	South Africa	Cattle	Anorexia, severe depression, ruminal, stasis, black soft feces, yellow discoloration of mucous membranes	Fourie et al. (1987)
	Florida, USA	Horses	Pinknose, colitis, liver bright yellow severe dermatitis	Morton (1994)
		Dogs	Vomiting blood, liver damage	
		Children (after eating unripe lantana berries)	Nausea, vomiting, abdominal pain dilated pupils	Wolfson and Solomons (1964)
	Texas, USA	Kangaroos	Anorexia, depression, jaundice, dermatitis of ear margins, eyelids, muzzle, opacity of corneas, liver was swollen, mottled and distended	Johnson and Jensen (1998)
	Cuba	Cattle	Dermatitis, jaundice, toxic hepatitis, neutrophilic leukocytosis, increased transaminases and urea levels	Alfonso et al. (1982)
	Mexico	Cattle, sheep	Depression, inappetance, constipation Decrease of ruminal movements, Icterus, erythema on exposure to light	de Aluja et al. (1970), de Aluja and Skewes (1971)
	South Africa	Boer goat kid	Severely icteric, dehydrated, constipated, hepatosis, distension of gall bladder, nephrosis	Ide and Tutt (1998)
	New Zealand	Cattle and sheep	Cholestasis, jaundice and photosensitization	Black (1981), Black and Carter (1985)
	Kukrail forests, Lucknow, India	Cattle	Anorexia, severe constipation, jaundice peeling of skin, photosensitization, heavy mortality	Yadava and Verma (1978)
	Nagpur, India	Cattle	Anorexia, dullness, peeling of skin, skin lesions only on non-pigmented area, affected skin highly necrosed	Aloni (1979)
	Rampur Busheir (H. P.), India	Sheep and goat	Anorexia, depression, yellowness of eyes, swelling of face and eyes	Katiyar (1981)
	Andhra Pradesh, India	Sheep	Became dull, avoided light, edema of ears, increased respiration, weakness of hind limbs, jaundice, constipated	Sreenivasulu et al. (1987)
	National Cattle Breeding Station, Belmont, Australia	Cattle	Hepatotoxic disease	Frisch et al. (1984)
L. camara var. *aculeata*	Allahabad (forest area, U.P. hills), India	Sheep	Anorexia, anaemic, mucous membranes icteric, color of urine dark yellow, swelling of ears, face and lips	Srivastava and Sinha (1980)
	Kangra valley (H.P.), India	Poisoning in cattle, buffaloes and sheep	Anorexia, constipated, swelling of face, muzzle became dry followed by excoriation, eyelids swollen and yellow in color, fissures appeared on muzzle, ear tips, severe jaundice	Sharma and Makkar (1981), Sharma et al. (1981c), Sharma (1994)
L. camara var. *nivea*	Mato Grosso and Rio de Janeiro States, Brazil	Cattle	Photosensitization with high mortality, recent transport to lantana infested areas and hunger as predisposing factors	Tokarnia et al. (1984)
L. glutinosa	Santa Catarina State, Brazil	Cattle	Hepatogenous photosensitization	Riet et al. (1984), Kellerman and Coetzer (1985)

2. Metabolism of the Toxins

Pass and coworkers (Pass et al., 1985) observed that the differences in the susceptibility of species to lantana toxins are due to the metabolism of RLA (**6**) to different metabolites in the liver. Sheep and female rats, susceptible to intoxication by RLA, synthesize one major metabolite, the structure of which is not yet known. Female rats also synthesize a glucuronide of RLA, which accounts for 30% of the two metabolites (Pass et al., 1985). On the other hand, male rats, resistant to RLA intoxication, synthesize a different metabolite, the structure of which is also not known. Periodically, when female rats become resistant to lantana intoxication, they synthesize a RLA metabolite similar to that in male rats (Pass et al., 1985). Metabolites of the RLA but not the parent compound were detected on the bile canalicular membrane in rats. This implied that the injury to liver cells was due to the action of metabolites rather than that of the parent compound and that the bile canalicular membrane was the site of primary injury in the hepatocytes (Pass et al., 1985; Pass and Goosem, 1982). Biotransformation and disposition of lantadenes in guinea pig as laboratory animal model has been investigated by Sharma and coworkers (Sharma et al., 1999, 2000). Oral administration of lantana leaf powder (6 g/kg body weight) induced cholestasis and the animals were sacrificed 48 h after dosing. The liver homogenate, bile, gallbladder, blood, urine, contents of gastrointestinal tract (GIT), and feces were analyzed for the principal hepatotoxin, namely, LA (**1**), its congeners, and its biotransformation products, by high-performance liquid chromatography (HPLC) (Sharma et al., 1997a). Lantadenes could not be detected in liver, bile, gallbladder, blood, and urine samples. LA, LB (**2**), and their reduced derivates, RLA and RLB (**7**) and two unidentified metabolites could be detected in the contents of lower GIT and feces (Sharma et al., 1999, 2000). In vitro incubation of lantana leaf powder with guinea pig cecal contents under anaerobic conditions caused biotransformation of LA (**1**) and LB (**2**) to RLA (**6**) and RLB (**7**), respectively (Sharma et al., 1999, 2000). Such biotransformation of lantadenes did not take place in cattle rumen liquor (Sharma et al., 2000). Enzymatic machinery for the biotransformation of lantana toxins in rats or guinea pigs has not been characterized. No information is available on whether lantana toxins are transferred to milk, placenta, or the offspring of the lantana-poisoned animals.

3. Liver Injury

Cholestasis, functionally defined as a cessation or impairment of bile flow, can lead to nutritional problems related to malabsorption of dietary fats and fat-soluble vitamins as well as to liver damage caused by accumulation of toxic compounds (Koopen et al., 1998). On the basis of mechanism, cholestasis is usually divided into extrahepatic and intrahepatic. Extrahepatic cholestasis occurs due to the obstruction of large bile ducts outside the liver, for instance, due to gallstones (Koopen et al., 1998). On the other hand, intrahepatic cholestasis corresponds to a biliary secretory failure caused by mechanisms located within the anatomical confines of the liver (Desmet, 1978). The cause of intrahepatic cholestasis lies either at the level of liver parenchymal cells or within canaliculi/intrahepatic ductules (cholangioles) and/or portal ducts (Koopen et al., 1998). Normally, biliary compounds are taken up from the blood at sinusoidal membrane, stored and metabolized in the hepatocytes, and secreted via the canalicular membrane into the bile. Impairment of any of these steps might influence the secretory rate and lead to cholestasis (Schwarz et al., 1977). Lantana toxins cause intrahepatic cholestasis with the inhibition of bile secretion without widespread hepatic necrosis (Seawright, 1964; Seawright and Allen, 1972; Pass et al., 1976, 1978b, 1979b). LA and icterogenin (**8**) have been shown in rabbits to inhibit hepatic transport of prophyrins, bile pigments and bromosulphthalein (Heikel et al., 1960). This kind of hepatic dysfunction was believed to resemble intrahepatic cholestasis (Seawright, 1965c). The elevated levels of conjugated serum bilirubin in cholestasis indicate that biliary secretion of this compound is more affected than its cellular uptake and conjugation (Schwarz et al., 1977). The intense and prolonged jaundice observed during lantana poisoning is preceded by appreciable hepatocellular damage (Swearight, 1965c). Significantly, lantana poisoning is characterized by damage to peripheral parenchymal cells of the liver, while the cells located around the central vein remain normal. Consequently, substances for excretion into bile pass into the sinusoids at the periphery of the lobule through the parenchymal cells, the membranes of which are no longer semipermeable to the biliary constituents (Seawright, 1965c). This canalicular-sinusoidal circulation of bile ensures marked retention of bile in the liver. Only a few such cells need to be affected for extensive regurgitation to occur, which is consistent with lantana poisoning (Seawright, 1965c).

Generally, intrahepatic cholestasis is accompanied by dilation of bile canaliculi, loss of microvilli, and alterations in enzyme activities and composition of the canalicular membrane (Seawright, 1965c; Simon and Arias, 1972, 1973; Phillips et al., 1983; Trauner et al., 1998). Kinetic analysis has revealed that in most cases of intrahepatic cholestasis, canalicular secretion step is rate-limiting for the overall process (Koopen, 1998). Impaired activity of Na^+, K^+-ATPase could be responsible for inhibition of bile acid independent fraction of bile flow (Schwarz et al., 1977). Lantana toxins inhibited the hepatocyte bile secretion but not the bile ductular secretion, as shown by decreased bile salt secretion, but retention of response to secretin, in lantana-poisoned animals (Pass et al., 1976). Intrahepatic cholestasis in lantana poisoning causes photosensitization due to retention of phylloerythrin (a degradation product of chlorophyll), which is normally excreted in bile (Rimington and Quin, 1934). This type of photosensitization (secondary or type III photosensitization), which is due to impaired hepatobiliary excretion, is also called hepatogenous photosensitization (Kellerman and Coetzer, 1985). Secondary or type III photosensitization is by far the most frequent type of photosensitivity observed in livestock. The photosensitizing agent phylloerythrin, derived from the breakdown

of chlorophyll by microorganisms present in the GIT, accumulates in the plasma due to impaired hepatobiliary excretion.

Jaundice in lantana poisoning is due to accumulation of bilirubin, as a result of inhibition of bile secretion, and not due to the failure to metabolize bilirubin (Pass et al., 1978b). The time course of disposition of RLA (**6**) has been investigated using RLA labeled with tritium (Pass and Goosem, 1983). Tritium-labeled RLA was administered into the portal vein of three anaesthetized sheep and bile was collected for the next 3.5–5.5 h. It was observed that 20–35% of the administered RLA appeared in bile during this period. In another experiment tritium-labeled RLA was injected into conscious sheep and bile was collected through a cannula for 1 week. Nearly 85% of the injected labeled RLA appeared in bile during that time after injection into the portal vein (Pass and Goosem, 1983). Interaction of the metabolites of lantana toxins with components of the bile canalicular membrane is reported to damage the membrane. ^{13}C-nuclear magnetic resonance (NMR) spectra of bile canalicular membrane indicated possible changes in the mobility of phospholipids in the membrane (Pass and Goosem, 1983). In sheep, structural damage to the canalicular membrane, characterized by deterioration in the microvilli, occurs within 6 h of ingestion of the plant, with the loss of Mg^{2+}-ATPase activity (Pass et al., 1978a, 1978b). Similarly, in rats intoxicated with RLA, loss of Mg^{2+}-ATPase and 5′-nucleotidase enzyme activities occurs within 4–6 h of dosing (Pass et al., 1981a). In sheep and rats, changes in the bile canalicular membrane are evident prior to the rise in serum bilirubin, implicating them in the initiation of cholestasis (Pass et al., 1981b). The canalicular plasma membrane (CPM) of guinea pigs administered partially purified lantana toxins had a decrease in protein content but marked increase in cholesterol and cholesterol:phospholipids ratio (Sharma and Dawra, 1984). The activity of Na^+, K^+-ATPase in CPM in lantana-intoxicated guinea pigs was significantly depressed but there was no significant alteration in the Mg^+-ATPase activity. The decrease in Na^+, K^+-ATPase activity may follow from the relative cholesterol enrichment of CPM. Inhibition of or rise in Na^+,K^+-ATPase in human erythrocytes has been observed by modulated high or low cholesterol levels (Yeagle, 1983). A decrease in the Na^+, K^+-ATPase activity has been incriminated in the impairment of bile secretion (Pass et al., 1976; Eakins, 1978). Another important feature of the CPM in lantana-poisoned guinea pigs was a marked increase in the activity of alkaline phosphatase (AP) and 5′-nucleotidase (Sharma and Dawra, 1984). It was not ascertained whether the observed alteration in CPM are a cause or consequence of choletatsis in lantana toxicity (Sharma and Dawra, 1984).

B. Clinical, Hematological, Histopathological, and Biochemical Aspects of Lantana Poisoning

1. Clinical Aspects and Gross Pathology

The clinical signs and gross pathology on administration of lantana leaf powder, partially purified toxins or pure toxins are summarized in Table 5. Typical signs of lantana toxicity include inappetance and constipation within 24 h of dosing followed by ictericity and photosensitization (Seawright and Allen, 1972; Sharma et al., 1980, 1992). The severity of ictericity depends on the dose (Gopinath and Ford, 1969). Both ruminants (sheep, cattle, and buffaloes) and nonruminants (guinea pigs, rats, and rabbits) have been used for experimental studies on toxicity of lantana leaf powder or isolated toxins (Table 5). Among the nonruminants, guinea pigs exhibited the most typical symptoms comparable to experimental or field cases of lantana toxicosis in ruminants (Sharma et al., 1980, 1987, 1988a, 1989, 1992). Liver is swollen, pale yellow, and fragile. The kidneys are also enlarged and yellow (Seawright and Allen, 1972). In guinea pigs administered lantana leaf powder or pure toxins the stomach was filed with gas, the subcutaneous layer of skin was yellow, and the gallbladder was invariably shrunken and its contents were dark opaque and viscous, unlike the bile of control animals, which is greenish yellow and transparent (Sharma et al., 1980, 1988a, 1991a, 1992).

2. Histological Lesions

a. Sheep. The early (24 h after dosing) degenerative changes in the liver following lantana intoxication involve the periportal parenchyma cells and spread to the centrally located cells with increase in the severity, resulting in extensive necrosis of parenchymal cells associated with hepatic excretory dysfunction (Seawright, 1964; Uppal and Paul, 1978). In chronically affected sheep (30 days after dosing), there is a tendency to sporadic vacuolation of the centrolobulary located cells with accumulation of bile pigments, while volume of hepatocytes does not change (Seawright, 1964). Hyperlasia of bile duct is found consistently (Seawright, 1964). Detailed electron-microscopic studies have been made on the hepatocytes of the sheep poisoned with lantana leaf powder or pure toxins (Seawright, 1965b; Seawright and Hrdlicka, 1977). There is separation of intercell parallel plasma membranes with microvilli like formation and some proliferative microvilliform structures become separated from the plasma membrane (Seawright, 1965b). On the other hand, canalicular membranes become enlarged and the microvilli more numerous, longer, and finger shaped. While some parts show complete absence of microvilli, others show loss of pericanalicular osmiophilia and the formation of bleb-like structures projecting into the canalicular lumen (Seawright, 1965b). Severely affected hepatocytes show fragmentation and dispersal of endoplasmic reticulum, large pinocytic vacuoles and lipoid deposits in many cells, granular and finely fibrillar dense material consisting of hypertrophic agranular reticulum in the ground substance of the cytoplasm, and proliferation of agranular endoplasmic reticulum that pushes other organelles to the periphery (Seawright, 1965b). The histological lesions in kidneys of sheep affected by lantana poisoning are fatty degeneration of proximal convoluted tubules, vacuolar degeneration of tubular epithelium of cortex, and cast formation in the

uriniferous tubules leading to cellular necrosis, followed by increased eosinophilia and pyknosis of nuclei in some nephrons of the convoluted tubules (Seawright, 1964). Patchy degeneration of heart muscle fibers with scanty petechial hemorrhages and fragility of myocardial fibers in the heart along with pulmonary edema and emphysema of the lungs was observed in lantana-poisoned sheep (Seawright, 1964). The gallbladder shows distension sometimes to as much as 30 times the normal, interstitial edema with polymorphonuclear and mononuclear inflammatory cell infiltration and atrophic as well as degenerative changes in the smooth muscle fibers in the bladder wall (Seawright, 1963). During lantana poisoning in sheep, paralysis of gallbladder has been demonstrated (Pass and Heath, 1977). The contraction of strip of sheep gallbladder in vitro in the presence of cholecystokinin, pentagastrin, and acetylcholine was inhibited by bile salts. However, only contraction to cholecystokinin was inhibited by lantadene A. Thus, it was inferred that gallbladder paralysis in lantana poisoning may be due accumulation of bile salts and LA (**1**) (Pass and Heath, 1977).

b. Cattle. In lantana-poisoned cattle the hepatocytes were markedly enlarged. The bile canaliculi appeared distended and contained yellow-brown bile plugs. The cytoplasm of the hepatocytes and swollen Kupffer cells contained brown staining droplets. There was extensive vacuolation of the hepatocytes to give a reticular appearance. The nuclei were enlarged and vesicular with marginal distribution of chromatin and prominent large nucleolus (Seawright and Sferco, 1966; Seawright and Allen, 1972; Pass et al., 1978b). Lytic necrosis of some liver cells, discontinuity of limiting plasma membrane, and fragmentation and dispersal of cytoplasmic organelles was observed by electron-microscopic studies (Seawright and Allen, 1972). Parts of bile canalicular membrane are without microvilli, and in some cells irregular bleb-like projections of the canaliculi into the lumen occur (Seawright and Allen, 1972). Cloudy swelling, fatty degeneration, portal fibrosis, hyperplasia of bile ducts, edema of gallbladder walls, parenchyma degeneration, hemorrhages, and feathery degeneration in liver have been reported on oral administration of *L. camara* leaves to cattle (da Silva and Couto, 1971; Dwivedi et al., 1971; Aguilera et al., 1986). Kidneys of lantana-intoxicated cattle show extensive vacuolation of tubular epithelium with pyknosis, necrosis of epithelium of proximal convoluted tubules, vacuolation of epithelium of Henle's loop, and distension of tubular lumen containing amorphous protein coagulum (Seawright and Allen, 1972).

c. Goats. *Lantana camara* poisoning in goats caused pulmonary edema, pneumonia with infiltration of mononuclear cells within the alveoli in the lungs, and necrosis and cytoplasmic vacuolation of hepatocytes, liver fatty changes, hemorrhage of intersinusoidal spaces, coagulative necrosis, cirrhosis, and proliferation of bile ductules in the liver. Kidneys had marked congestion, hemorrhage, and necrosis along with necrosis and pathological changes in the rumen, mesenteric lymph nodes, and skin (Obwolo et al., 1990, 1991; Ali et al., 1995).

d. Guinea Pigs and Rats. Seawright (1965a) was the first to study the effects of oral administration of lantana extract on guinea pigs. Pathological lesions were observed in heart, lungs, liver, gallbladder, and kidneys (Seawright, 1965a). The heart had subepicardial petechial hemorrhages; the lungs had pulmonary edema and were hemorrhagic. The liver had periportal vacuolar degeneration, mid zonal necrosis, bile ductule proliferation, portal fibrosis, and distension of lymphatics. The gallbladder showed hemorrhagic ulcers on the mucosal wall, and the kidneys had vacuolar degeneration of tubular epithelium and hyaline cast formation (Seawright, 1965a). Histopathological examination of the liver of guinea pigs intoxicated with LC (**3**) (form II) revealed swelling of hepatic cells, dilatation of bile canaliculi, vacuolation of hepatocytes, pyknosis of nuclei, and hydropic degeneration. Identical but less severe lesions were observed in the animals administered form I of LC (Sharma et al., 1992). The pathological lesions in female rats induced on oral administration of RLA (**6**) in olive oil, including swelling of hepatocytes and hyperplasia of bile ductules (Pass et al., 1979a).

e. Rabbits. Intoxication of rabbits by leaves of lantana (*L. camara*) caused degeneration and swelling of hepatic cells, portal fibrosis, bile canaliculi dilatation, biliary hyperlasia, desquamative, and necrotic changes in bile duct epithelium and biliary cirrhosis in the liver (Sharma et al., 1988c). The other features were tubular nephrosis, inflammatory interstitial reaction, nephrosclerosis, proliferation of mesenchymal cells in glomerular tufts, degeneration of tubules, swelling of tubular epithelial cells, and pyknosis of nuclei in the kidneys (Sharma et al., 1988c).

3. Hematology and Blood Chemistry

Oral administration of lantana leaf powder elicited a transient increase in the hematocrit values and number of neutrophils and a decline in number of thrombocytes in blood of sheep (Seawright, 1963). Increase in blood clotting time and hematocrit values and a decrease in erythrocyte sedimentation rate was observed in buffaloes and cattle (Dhillon et al., 1970; Hussain and Roychoudhury, 1992). Similarly, oral administration of crude lantadenes to sheep at a dose of 50 and 100 mg/kg body weight caused significant increase in coagulation time, prothrombin time and serum bilirubin content and decrease in erythrocyte sedimentation rate (Uppal and Paul, 1982). Increased sensitivity of erythrocytes to osmotic shock (Sharma et al., 1981c), a fall in packed cell volume, total erythrocyte count, hemoglobin, neutrophilia, and leukocytosis were observed in buffaloes and cattle in lantana poisoning (Hari et al., 1973; Alfonso et al., 1982; Kalra et al., 1984). Similarly, lantana poisoning in goats caused progressive decrease in packed cell volume, hemoglobin, total erythrocyte count, and an increase in leukocyte count and blood clotting time (Ali et al., 1995). Packed cell volume, however, showed an increase in merino lambs (McSweeney and Pass, 1983a). Intoxication of guinea pigs with lantana leaf powder elicited an increase

in hematocrit, erythrocyte and leukocyte number, hemoglobin, and urea (Sharma et al., 1982d). Enzyme activities of glutamate oxaloacetate transaminase (GOT), acid phosphatase (ACP), lactate dehydrogenase (LDH), glutamate dehydrogenase (GLDH), and sorbitol dehydrogenase (SDH) exhibited marked increase (Sharma et al., 1982d). Oral administration of LA (**1**) to guinea pigs elicited a marked increase in the activities of GOT, AP, ACP, LDH, SDH, and γ-glutamyltransferase (γ-GT) (Sharma and Sharma, 1999). There was no change in total serum protein but a marked increase in the level of γ-globulins in the sera of lantana-poisoned guinea pigs (Sharma et al., 1984). Dwivedi and coworkers (1971) observed a transient increase in total serum proteins in lantana-poisoned buffalo and cattle. Unlike guinea pigs, lantana poisoning in ruminants is prolonged for 1–2 weeks. An increase in immunoglobulins has been observed in primary biliary cirrhosis, a cholestatic condition (Sherlock and Scheuer, 1973). It is relevant to recall that animals that recover from the first exposure to lantana toxins have been found to be rather resistant to the toxic effects of subsequent encounters with the plant foliage (Sharma et al., 1984).

4. Biochemical Alterations

An increase in direct and total bilirubin value, where most of the bilirubin occurs in conjugated form, is one of the most consistent features of lantana poisoning in ruminants (Agarwala et al., 1962; Seawright 1963a; Gopinath and Ford, 1969; Dwivedi et al., 1971; Seawright and Hrdlicka, 1977; Sharma et al., 1980), along with an increase in the phylloerythrin levels (Gopinath and Ford, 1969). Guinea pigs intoxicated with lantana leaf powder, partially purified toxins, LA (**1**) or LC (**3**) had marked increase in conjugated form of bilirubin (Sharma et al., 1980, 1982d, 1991a, 1992; Sharma and Sharma, 1999).

a. Sheep. Intoxication by *L. camara* leaves did not elicit any change in the serum AP, GOT (Seawright, 1963), or glutamate pyruvate transaminase (GPT) (Seawright et al., 1963a; Gopinath and Ford, 1969; Dwivedi et al., 1971). Gopinath and Ford (1969) observed a sharp increase followed by a return to normal level in the activities of serum SDH, GOT, and arginase. Administration of LA in capsules or in dimethyl sulfoxide (DMSO) and RLA (**6**) and LB (**2**) in DMSO elicited an increase in plasma bilirubin and GOT within 24 h of dosing (Seawright and Hrdlicka, 1977). Intravenous administration of LA (**1**) also elicited a rise in plasma SDH and GOT with or without hyperbilirubinemia (Pass et al., 1979b).

b. Cattle. Oral administration of *L. camara* leaves elicited a rise in serum GOT, AP, GLDH, serum total protein, serum albumin, and serum globulin (Dwivedi et al., 1971; Aguilera et al., 1986), and a decrease in albumin/globulin ratio (Dwivedi et al., 1971). Seawright and Sferco (1966) observed a sharp rise in serum GOT activity in lantana-poisoned calves, which decreased by 12th day when the animal died. This trend was comparable to the serum enzymes profile in lantana-poisoned sheep (Gopinath and Ford, 1969).

c. Goats. *Lantana camara* intoxication elicited a rise in serum bilirubin, GOT, creatinine, γ-glutamyltranspeptidase, and blood urea nitrogen (Obwolo et al., 1990, 1991).

d. Guinea Pigs. Biochemical aspects of hepatic injury in guinea pigs induced by lantana poisoning have been studied extensively, wherein all the organelles were affected in a manner coincident with biochemical events in cholestasis induced by other agents (Sharma, 1984). Biochemical changes in different organelles on intoxication of guinea pigs with *L. camara* leaf powder or partially purified toxins are described in the next section.

5. Intracellular Aspects

Macromolecular Constituents. Oral administration of lantana leaf powder (2 g/kg on 3 consecutive days) caused a decrease in hepatic and renal tissue dry weight, DNA, and protein contents. DNA alterations in the kidneys appear to be due to the swelling of the tissue, because there was no significant change in DNA content of kidneys on the dry weight basis. On the other hand, the hepatic DNA content had a marked decrease when the data were expressed on dry weight basis (Sharma et al., 1981a). Seawright and Sferco (1966) have also noticed nuclear lesions in lantana poisoning in calves. DNA exists in two forms, stable and metabolic; the latter offers extra copies of genes and is subject to wear and tear (Pelc, 1968). The observed decrease in DNA content of liver might be a cumulative effect of increase in tissue water content and loss of metabolic DNA. Hepatic as well as renal RNA levels relative to dry matter content of the tissues exhibited an increase. This implies that unlike DNA, metabolism of RNA is not adversely affected during lantana poisoning (Sharma et al., 1981a).

Mitochondria. There was a marked increase in liver mitochondria in cholesterol:protein ratio and cholesterol: phospholipid molar ratio, a decrease in the hepatic mitochondrial protein, and no change in the phospholipid: protein ratio on lantana intoxication with *L. camara* leaf powder (Sharma et al., 1982b). Activities of succinic dehydrogenase, cytochrome oxidase, Mg^{2+}-ATPase, and GLDH increased, while the activity of NADH-ferricyanide reductase did not alter, implying that the outer mitochondrial membrane is not affected during lantana intoxication (Sharma et al., 1982b).

Microsomes. The observations on hepatic microsomes on lantana toxicity induced by oral administration of lantana leaf powder were a decrease in protein content, phospholipid:protein ratio, and cholesterol:protein ratio, while cholesterol:phospholipid molar ratios did not change, implying that the fragments of the lipid bilayer of endoplasmic reticulum become dissociated from the microsomes, independent of the protein moieties (Sharma et al., 1982c). Enzyme activities of aniline hydroxylase, aminopyrine *N*-demethylase, NADH-cytochrome *c* reductase, NADH-ferricyanide reductase, UDP-glucuronosyl transferase, and cytochrome P-450 decreased, while the activity of NADPH-cytochrome *c* reductase did not change, implying

an impairment of the microsomal electron transport chain and drug metabolism system (Sharma et al., 1982c). Activities of Mg^{2+}-ATPase and Na^{+},K^{+}-ATPase increased while the activity of 5′-nucleotidase did not change in hepatic microsomes in lantana toxicity (Sharma et al., 1982c).

Lysosomes and Cytosol. Hepatic lysosomal enzymes, acid phosphatase, cathepsin B, and deoxyribonuclease II activities in the homogenate did not change, while these enzymes exhibited marked increase in the postmitochondrial fractions (Sharma et al., 1983). An increase in the ratios of these enzyme activities in the postmitochondrial fraction to the whole homogenate was observed, which implied leakage of the lysososmal enzymes in lantana toxicity (Sharma et al., 1983). Cytosolic enzyme activities of xanthine oxidase, hexokinase, aldolase, lactate dehydrogenase, and glucose-6-phosphate dehydrogenase exhibited marked increase. An increase in the activity of xanthine oxidase could cause tissue injury through higher production of superoxide radicals (Sharma et al., 1983). A decrease in the cytosolic glutathione *S*-transferase, which conjugates glutathione with a variety of electrophilic compounds including bilirubin, would make the liver more susceptible to the toxic action of bilirubin (Sharma et al., 1983).

Lipid Peroxidation. Lipid peroxidation was inhibited in all the tissues of lantana-poisoned guinea pigs in the order adrenals > liver > kidneys > heart > lungs > testes > brain, where the inhibitory factor was associated with the postmitochondrial fraction (Sharma et al., 1982a). Bilirubin also inhibited lipid peroxide formation in guinea pig liver homogenate (Sharma et al., 1982a). Subsequent workers provided unequivocal evidence that bilirubin is an important nonprotein antioxidant of physiological significance (Stocker et al., 1987; Dudnik, 2001; Davies et al., 2005). Free radical reactions and peroxidation of biomembrane constituents have been found in a number of biochemical functions of the cells, for example, prostaglandin synthesis, destruction of bacteria by granulocytes, metabolism of xenobiotics, ion transport across membranes, and self-renewal of biomembranes (Vladimirov, 1972; Willson, 1978). One possibility is that inhibition of lipid peroxidation in lantana poisoning may be adding to tissue injury by interfering with one or more of the normal biochemical processes of the cell. Another counterargument is that spreading of the bilirubin to the various tissues in lantana poisoning provides a sort of antioxidant defense against free radical damage in lantana-induced hepatotoxicity (Tomaro et al., 2002).

6. *Other Aspects*

Crude lantadenes isolated from *L. camara* caused marked ECG changes in sheep 12 h after dosing, with an increase in heart rate, decrease in duration of S-T segment, P-R interval, Q-T interval, and QRS complex, and an increase in the amplitude of P and T waves (Uppal and Paul, 1972). Administration of *L. camara* leaf powder suspended in water (200 mg/kg body weight for 110 days) to sheep caused immunosupression. There was significant reduction in cellular and humoral immunity and phagocytic activity of splenic reticulo-endothelial cells (Ganai and Jha, 1991). The animals did not develop any signs of ictericity that characterize lantana poisoning. Methanolic extract of aerial parts of *L. trifolia* produced bronchodilation of isolated guinea pig trachea comparable with that of salbutamol, reduced bronchoconstriction of isolated guinea pig trachea induced by histamine, 5-hydroxytryptamine, or acetylcholine, and caused neuromuscular blocking of rat phrenic nerve diaphragm which could not be inhibited by physostigmine (Achola and Munenge, 1996). Administration of leaf juice from *L. camara* to male rats at the dose of 60, 300, 600, and 1500 mg/kg body weight elicited reduction in absolute and percent lymphocyte count, a significant hypoglycemic effect at high dose, and a significant inhibition in formation of granulomatous tissue but no clinical signs of lantana toxicity like jaundice (Garg et al., 1997).

C. Treatment of Lantana Poisoning

Lantana poisoning causes ruminal stasis and toxicity due to continuous absorption of the toxins from the rumen. The poisoning was treated surgically by rumenotomy followed by removal of rumen contents and replacement with fresh rumen contents (McSweeney and Pass, 1982; McSweeney, 1988). However, this treatment would be uneconomical when large numbers of animals are affected. Administration of activated charcoal to sheep (500 g in 4 L of electrolyte) and to cattle (2.5 kg in 20 L of electrolyte) in the early phase of intoxication, checked the rise in plasma bilirubin, and successfully treated the affected animals (Pass and Stewart, 1984; McSweeney, 1988). However, this treatment should be started before the onset of absorption of the toxins. Administration of activated charcoal at the rate of 5 g/kg body weight in water + electrolyte administered by stomach tube to cattle (McLennan and Amos, 1989) and activated charcoal (5 g/kg body weight) as oral dose supplemented with dextrose injection and vitamin B complex and liver extract (belamyl) to goats facilitated recovery of the animals (Ali et al., 1996). Administration of bentonite (5 g/kg body weight) has potential as a cheaper alternative to activated charcoal for curing lantana-poisoned calves, though the animals take a little longer to recover as compared to treatment with activated charcoal (McKenzie, 1991). Treatment of lantana-poisoned calves using Tefroli powder (containing the plant *Tephrosia purpurea* as the main ingredient) proved to be effective (Bahadure et al., 1992). Sporadic efforts have been made to use oleogenic purgatives, presumably to flush out the lantana ingested along with the released toxins (Sharma et al., 1981b). Treatment of lantana-poisoned sheep with linseed oil, Glauber's salt, bethanechol, or intravenous therapy failed to restore reticuloruminal motility and the animals succumbed to continuous illness (McSweeney and Pass, 1982). Administration of glucose saline, anthisan, liver extract, and an herbal preparation Liv-52 to lantana-poisoned buffalo calves prolonged the period of survival of the affected animals only marginally (Hari

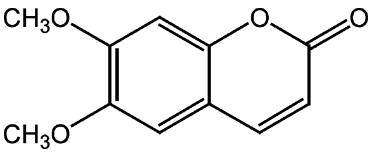


FIG. 2. Chemical structure of 6,7-dimethylesculetin, the active constituent in Chinese herbal tea Yin Zhi Huang which activates hepatic nuclear receptor, CAR and enhances bilirubun clearance.

et al., 1973). Enzymatic removal of bilirubin from blood using bilirubin oxidase is a potential treatment for jaundice (Lavin et al., 1985; Soltys et al., 1992). This technique would be uneconomical for treating large animals due to the large volume of blood involved. Yin Zhi Huang (YZH, an herbal tea), a decoction of Yin Chin (*Artemisia capillaris*) and three other herbs, is widely used to prevent and treat neonatal jaundice (Huang et al., 2004). YZH is now shown to activate constitutive androstane receptor (CAR, NR1I3) in liver, which enhances the clearance of bilirubin (Lazar, 2004; Huang et al., 2003, 2004; Elferink, 2004). The active constituent in the YZH is 6,7-dimethylesculetin (Figure 2) (Lazar, 2004). 6,7-Dimethylesculetin binds to and activates the hepatic nuclear receptor CAR and its target genes, including CYP 2B10, leading to increased bilirubin clearance (Lazar, 2004). It would be worthwhile to study the effect of Yin Zhi Huang or the active constituent 6,7-dimethylesculetin (Figure 2) in lantana-affected animals to evaluate its ameliorative effects.

Vaccination against plant toxins is another method of protection against plant toxicosis (Edgar, 1994; Filipov et al., 1998; Lee et al., 2003). Injection of LA (**1**) and LB (**2**) conjugates of bovine serum albumin and hemocyanin to sheep and cattle produced antibodies against both the lantadenes. The vaccinated animals were administered lantadene A or lantana leaf powder. Cholestasis was less severe in the vaccinated animals as compared to the unvaccinated control group (Stewart et al., 1988; Pass and Stewart, 1992). One of the elegant ways to combat toxicosis by plant toxins in animals is to isolate the microorganisms with the capacity to degrade the toxins and establish them in the rumen (Jones and Lowry, 1984; Jones and Megarrity, 1986; Gregg et al., 1994; Gregg, 1995). Thus, any subsequent exposure to the plant foliage degrades the toxins. The feasibility of introducing a new bacterium into the rumen and thereby reducing the toxicity of a naturally occurring toxin has been demonstrated for mimosine (the toxin of *Leucaena leucocephala)* and fluoroacetate (the toxin of *Gastrolobium* and *Oxylobium* spp.) toxicity (Jones and Lowry, 1984; Gregg, 1995; Gregg et al., 1994, 1998). Isolation of bacterial strains *Pseudomonas picketii*, *Alcaligenes faecalis*, and *Alcaligenes odorans* capable of biodegradation of LA offers potential for treatment of lantana poisoning after establishment in rumen (Sharma et al., 1997b; Singh et al., 1999, 2000, 2001; Allison and Ramussen, 1992; Gregg, 1995; Gregg et al., 1994, 1998).

V. BIOMEDICAL APPLICATIONS

Research on bioactive constituents of poisonous plants has been extremely useful to design management strategies to prevent economic losses on account of toxicosis (James et al., 2004). The other aspect is the biomedical applications of the extracts or pure natural products of poisonous plants (James et al., 2004). Lantana, though a poisonous plant, finds a conspicuous place in the list of medicinal plants as well (Ross, 1999). The various bioactivities of extracts or isolated compounds are described next.

A. Antimicrobial Activity

Antifungal activity: Leaves of *L. camara* have been utilized for inhibition of spore germination in *Alternaria alternata*, *Aspergillus niger*, *A. fumigatus*, and *Mucor mucedo* (Ross, 1999; Saxena and Tripathi, 1985). Fungitoxic activity of *L. camara* has also been reported against *Alternaria solani, Aspergillus sydowii*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Helminthosporium oryzae*, and *Pyricularia oryzae* (Chauhan and Joshi, 1990; Ganguly, 1994; Mishra et al., 1988). Ointment made with ethanolic extracts of leaves of *L. camara* applied as topical treatment on chronic crusty or acute lesions of bovine dermatophilisis induced healing in 3–4 days. There was no recurrence of the disease for more than three years (Ali-Emmanuel et al., 2003).

Antibacterial and antiviral activity: Antibacterial activity of *L. camara* has been reported against *Bacillus subtilis*, *Escherichia coli*, *Micrococcus pyrogenes* var. *aureus*, *Pseudomonas aeruginosa,* and *Staphylococcus aureus* (Verpoorte and Dihal, 1987). Aqueous extract of flowers of *L. indica* induced resistance in *Chenopodium amaranticolor* against the potato virus X (Rao et al., 1985). Hexane extract of *L. hispida* inhibited the growth of *Mycobacterium tuberculosis* H37Tv and was also active against multidrug-resistant clinical isolates of tuberculosis (Jimenez-Arellanes et al., 2003). The essential oil of *L. achyranthifolia* obtained by steam distillation was active against *Shigella boydii*, *Staphylococcus aureus, Staphylococcus epidermidis, Bacillus subtilis*, *Sarcina lutea*, *Vibrio cholerae*, *Escherichia coli*, *Enterobacter agglomerans*, *Enterobacter aerogenes, Yersinia enterocolitica,* and *Salmonella typhi* (Hernandez et al., 2005).Essential oil obtained from the aerial parts of *L. xenica* Mold (Verbenacea) inhibited the growth of *Bacillus cereus* and *Proteus mirabilis*. Both the bacteria were inhibited by (*E*)-caryophyllene as well, the major constituent of the essential oil (Juliani et al., 2002). Lantic acid isolated from *L. camara* was found to possess strong antibacterial activity against *Escherichia coli* and *Bacillus cereus* (Saleh et al., 1999). Essential oil of *L. camara* tested against seven bacteria and eight fungi showed a wide spectrum of antibacterial and antifungal activities. Among the organisms tested, *Pseudomonas aeruginosa*, *Aspergillus niger*, *Fusarium solaniand*, and *Candida albicans* were more sensitive (Deena and Thoppil, 2000). LA (**1**), LC (**3**), and related triterpenoids from the leaves of

L. camara inhibited Epstein–Barr virus activation (Inada et al., 1995).

Antiparasitic activity: Chemical constituents (lantanilic acid, camaric acid, and oleanolic acid) isolated from methanolic extract of the aerial parts of *L. camara* caused 98%, 95%, and 70% mortality, respectively, against root-knot nematode *Meloidogyne incognita* at 0.5% concentration. A standard nematicide furadan showed 100% mortality at this concentration (Begum et al., 2000; Qamar et al., 2005). Root bark extract of *L. camara* exhibited antimalarial activity against the multidrug-resistant K1 strain of *Plasmodium falciparum* (Weenen et al., 1990).

B. Medicinal Properties

Lantana is considered antiseptic, antispasmodic, carminative, and diaphoretic (Parrotta, 2001). The bark of stems and roots of *L. camara* contain a quinine-like alkaloid lantanine with strong antipyretic and antispasmodic properties (Sastri, 1962). Anti-inflammatory, antipyretic, and analgesic properties of extracts of *L. camara* leaves have been reported (Forestieri et al., 1996). *Lantana trifolia* extracts exhibited anti-inflammatory and analgesic effects (Uzcategui et al., 2004; Silva et al., 2005).

Mouse skin papillomas and mouse hepatic tumors were inhibited by LA (**1**) and LB (**2**) isolated from *L. camara* leaves (Inada et al., 1997). Verbascoside isolated from the leaves of *L. camara* exhibited inhibition of protein kinase C and antitumor activity (Herbert et al., 1991). Oleanolic and ursolic acids occurring in the stems, leaves, and roots of *L. camara* and *L. tiliaefolia* have application as oral drug for human liver disorders, as antihyperlipidemic and as anti-tumor-promotion agents (Liu, 1995, 2005). Twenty pentacyclic triterpenoids of the oleanane, ursane, and lupane group and their transformation products from *L. camara* and *L. indica* exhibited antimicrobial activity against several pathogenic and nonpathogenic bacteria and fungi (Verma et al., 1997). The remarkable antimotility effect of *Lantana camara* methanolic extract (LCME) against neostigmine as promotility agent points toward an anticholinergic effect due to *Lantana camara* constituents and attests to its possible utility in secretory and functional diarrheas and other gastrointestinal disorders. This effect was further confirmed by significant inhibition of castor oil-induced diarrhea in mice by various doses of LCME (Sagar et al., 2005). There is a great interest in identifying compounds that can selectively inhibit serine proteases (e.g., thrombin, human leukocyte elastase) for potential therapeutic benefits in thrombic disorders and treatment of emphysema and chronic bronchitis (Tapparelli et al., 1993). Methanolic extracts prepared from the leaves of *L. camara* have been found to inhibit human thrombin. An assay in which thrombin activity is measured as a function of clot formation from fibrinogen was used to guide the fractionation and purification of active constituents (**46**), which were characterized as 5,5-trans-fused cyclic lactone-containing euphane triterpenes (O'Neill et al., 1998). Synthesis of a variety of 5,5-trans-fused lactones, related to compounds found in extracts of *L. camara*, provided a series of novel acylating inhibitors of human thrombin, trypsin, chymotrypsin, and human leukocyte elastase (Finch et al., 1998). Proflavin displacement studies showed the inhibitors to bind at the active site of α-thrombin and α-chymotrypsin (Weir et al., 1998). Triterpenoids are at present receiving a lot of attention for development of novel anticancer (Setzer and Setzer, 2003; Baglin et al., 2003; Fernandes et al., 2003; Sharma and Sharma, 2006), antibacterial (Nick et al., 1994, 1995; Xie et al., 2005), anti-HIV (Fujioka et al., 1994; Kashiwada et al., 1998; Ito et al., 2001), and anti-inflammatory agents (Weniger et al., 2005; Kim et al., 2005; Jung et al., 2005), and modulators of transforming growth factor β/Smad signaling (Suh et al., 2003). Triterpenoids inhibit the activity of DNA polymerase and topoisomerases, biochemical targets for anticancer compounds (Mizushina et al., 2000; Wada et al., 2001, 2002; Wada and Tanaka, 2005). Drug discovery based on natural products of lantana is a very exciting current area in view of the presence of a wide spectrum of triterpenoids in different parts of lantana plant (Table 3, Figure 1).

VI. CONCLUSION

The global dimension of lantana problem as a weed as well as toxicity in grazing animals has been well documented (Tables 1 and 6). The domination of lantana over other species is due to its allelopathic action. The allelochemicals of lantana plant are phenolics and triterpenoids. Lantana toxicity has been reproduced in experimental animals by administration of leaf powder, partially purified material, and pure toxins. The main hepatotoxin is lantadene A (**1**), a pentacyclic triterpenoid. The congeners of lantadene A play a minor role in lantana toxicosis. Based on x-ray diffraction studies, the lesser hepatotoxic potential of lantadene B (**2**) has been ascribed to steric hindrance of two methyl groups at C33. Continuous absorption of the toxins is required for hepatotoxicity to be maintained over a long period of time. Ruminal stasis is an important feature of lantana poisoning. It has been attributed to the inhibitory neural impulses arising from liver injury. Typical signs of lantana toxicity are inappetance, constipation, jaundice, and photosensitization (Tables 5 and 6). There is marked increase in serum bilirubin, especially of the conjugated type. Similarly, the serum enzymes which typify liver injury also increase within 24–48 h of dosing with lantana leaf powder or isolated toxins. On necropsy, liver has been observed to be swollen, pale yellow, and fragile. The kidneys are also enlarged and yellow. The histological lesions in liver of lantana-poisoned animals are consistent with intrahepatic cholestasis and hepatotoxicity. Intracellular organelles of liver, like mitochondria and microsomes, and the canalicular plasma membrane (CPM) have marked cholesterol enrichment in lantana poisoning. A decrease in CPM Na^+,K^+-ATPase appears to be the primary reason for decrease in bile flow, regurgitation, and the resulting cholestasis. Symptomatic treatments for lantana toxicity work well if the animal is brought to the clinician

within 24 h. Two approaches for the rational therapy are vaccination and biodegradation of the toxin in the rumen to nontoxic compounds. Vaccination against lantana toxicity has been tried with limited success. No anaerobes have been obtained with capacity to degrade lantana toxins. The successful detoxification of mimosine (the toxin of *Leucaena*) and monofluoroacetate (the toxin in *Gastrolobium* and *Oxylobium* spp.) is a motivation to work on the ruminal detoxification of lantana toxins using tools of biotechnology. Thus, future studies are warranted for development of a rational therapy against lantana toxicity using immunological and biotechnological approaches.

Natural products chemistry of lantana has received a lot of attention over the last six decades (Tables 3 and 4, Figure 1). This, in turn, has spurred research on biomedical application of lantana compounds. This is more exciting in view of the presence in sizeable amounts of a spectrum of triterpenoids in different parts, especially leaves of lantana plant (Table 3). Triterpenoids at present are receiving a lot of attention for development of novel anticancer, antibacterial, anti-HIV, and anti-inflammatory agents, and modulators of transforming growth factor β/Smad signaling. Thus, biomedical research for drug development using triterpenoids as well as the other natural products of lantana, like flavonids, iridoids, phenylpropanoids, and furanonaphthoquinones, is an attractive area of interface between toxicology, chemistry, and medicine.

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