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Review

Lantana camara L. (Verbenaceae)

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Abstract

Lantana camara L. is regarded both as a notorious weed and a popular ornamental garden plant and has found various uses in folk medicine in many parts of the world. Some taxa of the widely variable *L. camara* complex are toxic to small ruminants and this effect has been associated with the types and relative amounts of some triterpene ester metabolites. However, *L. camara* also produces a number of metabolites in good yields and some have been shown to possess useful biological activities. All these aspects are considered in this review to allow an evaluation of the potential for utilisation of the large biomass of *Lantana* available. The phytochemistry of other members of the *Lantana* genus is included.

Keywords: *Lantana camara*; Toxicity; Triterpenes; Iridoid glycosides; Furanonaphthoquinones; Flavonoids; Phenylethanoid glycosides; Bioactivity

1. Introduction

The genus *Lantana* (Verbenaceae) as described by Linnaeus in 1753 contained seven species, six from South America and one from Ethiopia [1]. *Lantana* (from the Latin *lento*, to bend) probably derives from the ancient Latin name of the genus *Viburnum* which it resembles a little in foliage and inflorescence. *Lantana* is

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Fig. 1. *Lantana camara* L. (photo courtesy of Dr R. Randall, Weed Science Group, Agriculture, Western Australia).

mostly native to subtropical and tropical America, but a few taxa are indigenous to tropical Asia and Africa. It now occurs in approximately 50 countries where several species are cultivated under hundreds of cultivar names. The recorded number of *Lantana* species varies from 50 to 270 specific and subspecific entities, but it appears that a better estimate is 150 species. The genus is a difficult one to classify taxonomically since species are not stable and hybridisation is widespread, shape of inflorescence changes with age, and flower colours vary with age and maturity [1].

Lantana camara L., commonly known as wild or red sage, is the most widespread species of this genus, growing luxuriantly at elevations up to 2000 m in tropical, sub-tropical and temperate regions [2]. The species name, *camara*, is probably adopted from the West Indian colloquial name for the common species [3]. It is a woody straggling plant with various flower colours, red, pink, white, yellow and violet (Fig. 1). The stems and branches are sometimes armed with prickles or spines.

The plant is native to tropical and subtropical America. Dutch explorers introduced it into the Netherlands from Brazil in the late 1600s and later explorers from other countries brought seeds to Europe, Great Britain and North America. Following its introduction into Hawaii as a garden flower, it soon spread to the islands of the Pacific, Australia and southern Asia. In a similar way, from Natal it was rapidly spread by birds to the warmer areas of South Africa. In the 18th and 19th century, nurserymen commercialised and popularised many colourful forms

and it is now cultivated world-wide as an ornamental plant. Of the 650 cultivar names in the genus, the majority are associated with the *L. camara* complex. The plant is an aggressive, obligate outbreeder weed that has invaded vast expanses of pastures, orchards and forest areas in many tropical and subtropical regions. It has been estimated that 4 million hectares in Australia [1,4] and 160 000 in Hawaii [4] are infested with *L. camara*. It has been regarded as one of the 10 most noxious weeds in the world [2] and much has been written on its encroaching habit, methods of eradication and control [1–3,5,6].

Apart from its popularity as a garden plant, *L. camara* is said to form a useful hedge and to provide a good preparation for crops, covering the ground with a fine leaf mulch [1]. It improves the fertility of rocky, grave, or hard laterite soils, enriches the soil, serves to retain humus in deforested areas and checks soil erosion. It can serve to nurse the parasitic sandalwood seedlings and in the Pacific islands has been used as a support for yam vines. *Lantana* leaves and twigs are often used in India as a green mulch. The ash is rich in potassium and manganese which is useful in manuring coconut trees. The plant is not readily eaten by cattle unless pasturage is very scarce. In tropical countries, the ripe blue–black berries are eaten, but ingestion of the green berry has led to human fatalities [4,6].

In this review, the ethnopharmacology, phytochemistry and toxicity of *L. camara* are considered. The biological activities exhibited by some of the metabolites available from *L. camara* are discussed and the results of recent studies on the triterpene inhibitors of human α-thrombin discovered in this plant are presented. This information provides a basis for the evaluation of *L. camara* as a useful source of renewable material.

2. Ethnopharmacology

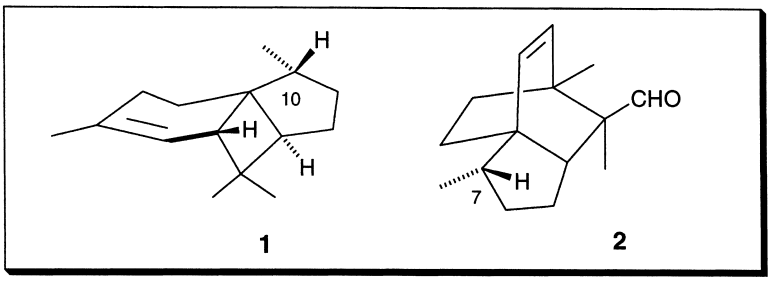
The plant has been used in many parts of the world to treat a wide variety of disorders [4]. *Lantana camara* found use in folk remedies for cancers and tumours. A tea prepared from the leaves and flowers was taken against fever, influenza and stomach-ache. In Central and South America, the leaves were made into a poultice to treat sores, chicken pox and measles. Fevers, cold, rheumatisms, asthma and high blood pressure were treated with preparations from the plant. In Ghana, infusion of the whole plant was used for bronchitis and the powdered root in milk was given to children for stomach-ache [7]. In Asian countries, leaves were used to treat cuts, rheumatisms, ulcers and as a vermifuge. Decoctions were applied externally for leprosy and scabies. It has been claimed that a steroid, lancamarone, from the leaves exhibited cardiotonic properties [8] and that lantamine, an alkaloid from the stem bark and roots showed antipyretic and antispasmodic properties comparable to those of quinine [9], but the validity of these claims has not been confirmed. From the leaves, an alkaloid fraction which lowered blood pressure, accelerated deep respiration and caused shivering in dogs was isolated and it was suggested that it may be useful in reducing fevers, and as a treatment of asthma and hypertension [10].

3. Phytochemistry

The phytochemistry of *L. camara* has attracted considerable interest mainly arising from the presence of toxic compounds in certain races. However, a number of phytochemical reports do not specify the variety investigated and others refer to various taxa using varietal epithets. The ease with which this plant hybridises introduces other variables making comparisons difficult. *Lantana camara* sensu latu is a complex of many closely related plant taxa and it is considered here as one species complex.

3.1. Mono- and sesquiterpenes

The early work on *Lantana* spp was concerned with studies on the essential oils although they are not high yield producers; for *L. camara*, the maximum yield obtained by hydrodistillation from the leaves reached 0.2% and, from the flowers, up to 0.6% [11,12]. The oil is available commercially and recently several studies have investigated the composition of samples of different origins. A sample obtained from *L. camara* trees grown in Brazil had a terpene-like, leathery, fatty, and sweaty odour. The constituents were found to be mainly (65%) bisabolene derivatives with only traces of monoterpenes. The sesquiterpenes present were β-curcumene (1.5%), (*E*)-nuciferal and (*Z*)-nuciferol (3.9%), (−)-*ar*-curcumen-15-al (5.6%), γ-curcumene (8%), *ar*-curcumene (9.7%), (−)-*epi*-β-bisabolol (∼ 10%), (−)-γ-curcumen-15-al (14.9%). Interestingly, the oil contained compounds (5%) which incorporate the new italicene skeleton (**1**), as epimers at C10, and 7.2% of the helifolene aldehydes (**2**), as epimers at C7 [13,14]. Safrole (1.8%) was the only other significant compound present. Noticeable differences in composition were observed with samples obtained from different locations in Brazil [15]. By way of comparison, oil from Anjouan (Comoro Archipelago) contained mainly humulene (22%) and caryophyllene (15%), and from Reunion, caryophyllene (35%) and davanone (15%). Samples from Madagascar and Central India were more variable both in the relative amounts of monoterpenes to sesquiterpenes and in the variety of these [14,16,17]. Subcritical liquid extraction with CO_2 has been used to recover



the volatile oil from *L. camara* [18]. Yields increased from 0.2% obtained by hydrodistillation to 1.84% on extraction with carbon dioxide.

3.2. Triterpenes

The initial work on the triterpenes was concerned with the structural elucidation of lantadene A (**3**) and B (**4**), the first recognised toxic compounds from *L. camara* [20]. It soon became evident that the content of these two compounds varied; a sample from Australia yielded both, another one gave lantadene A and only traces of B, whereas a South African sample gave no crystallisable triterpenes [19,21]. In a detailed study of toxic taxa of *L. camara*, it was found that lantadene A and B predominated (up to 2.2% of the dry weight of leaves and stem; approx. ratio 2:1) [19]. In the course of these and other studies, a number of other triterpenes were identified and these are represented in Figs. 2 and 3 [19–37]. Most interest has been shown in the presence of lantadene A (**3**), B (**4**), C (**6**) [28] and D (**7**) [29] and reduced lantadene A (**9**) because of their demonstrated or suspected toxicity. Lantanolic (**14**) and lantic acid (**26**), originally isolated from an Indian sample of *L. camara*, incorporate an oleanane and an ursane skeleton with an unusual hemiketal arrangement between an alcohol at C-25 and the ketone at C-3 [22,23]. The lupeol analogue **30** of lantanolic and lantic acids has also been isolated [19].

The material on the surface of the leaves (exudate) is a mixture of flavonoids, lantadene A and icterogenin (**17**) [36]. In the roots of both toxic and non-toxic taxa, oleanolic acid (**8**) was the major constituent [19] and, in fact, the rootlets and root bark of *L. camara* provide a plentiful (2%) supply of oleanolic acid [37].

The structures assigned to the various triterpene metabolites were determined by classical methods and chemical correlation. Furthermore, X-ray crystallographic studies supported the structures assigned to lantadene A [38,39], B [40] and C [40,41]. A method for the TLC separation of lantadene A–D [42] and an HPLC method for the quantitation of the lantadenes [43] have been reported.

A recent investigation of the methanolic extract of *L. camara* has revealed a suite of euphane triterpene lactones. The presence of these metabolites, which occur in trace quantities (0.00004–0.0002%) [44], was detected by using an assay in which thrombin activity was measured as a function of clot formation from fibrinogen. In all, five active principles (**31–35**) were isolated. The structure of these compounds was determined by means of spectroscopic methods and confirmed by single crystal X-ray crystallographic studies on **31**. All compounds were potent inhibitors of human thrombin (IC_{50} 18–130 nM) and showed comparable activity to hirudin (IC_{50} 12 nM), a dried and refined extract of leeches (*Hirudo medicinalis*) [44].

3.3. Iridoid glycosides

A number of iridoid glycosides have been isolated from *L. camara*. The white, pink and red flowering taxa produced significant quantities of theveside (**36**) which

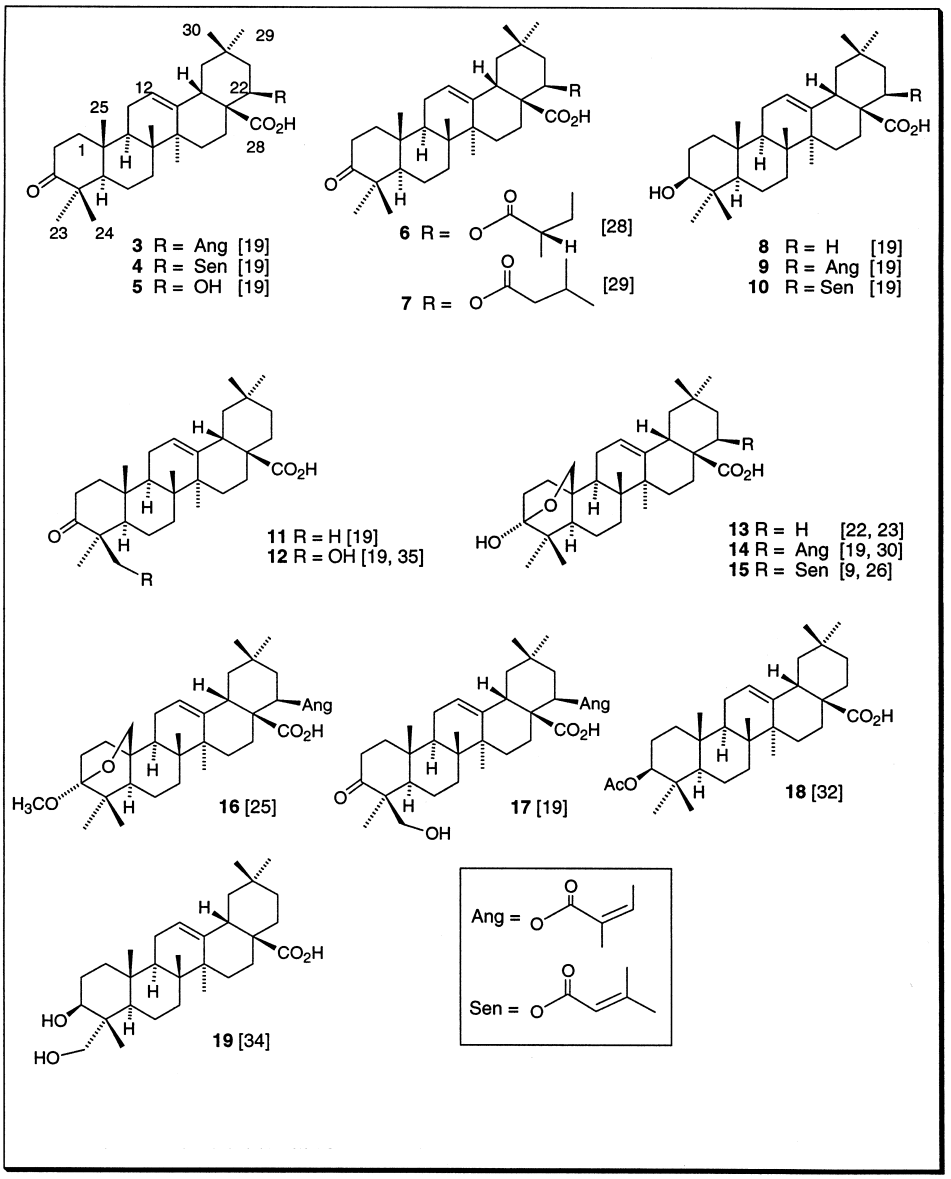


Fig. 2. Oleanolic acid derivatives isolated from *L. camara*.

was present as the sodium salt [45]. Quantitative estimation of the iridoid indicated that the stems contained up to 5.8% of the dry weight (red) in spring and 4.3 (white) and 4.9% (pink) when harvested in summer. Levels in leaves varied from 1.0–3.6% in spring and summer, and declined significantly (< 0.6%), in both leaves

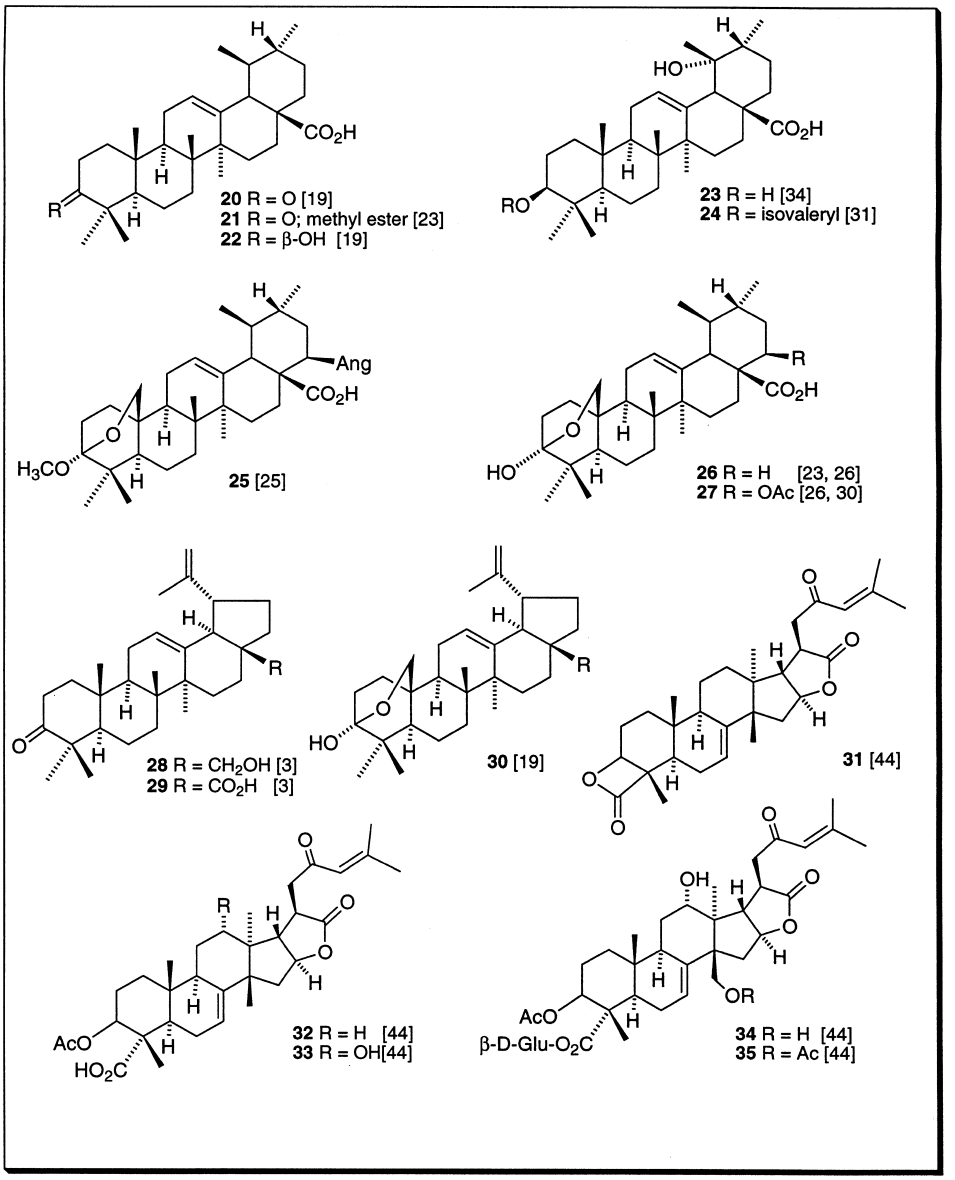
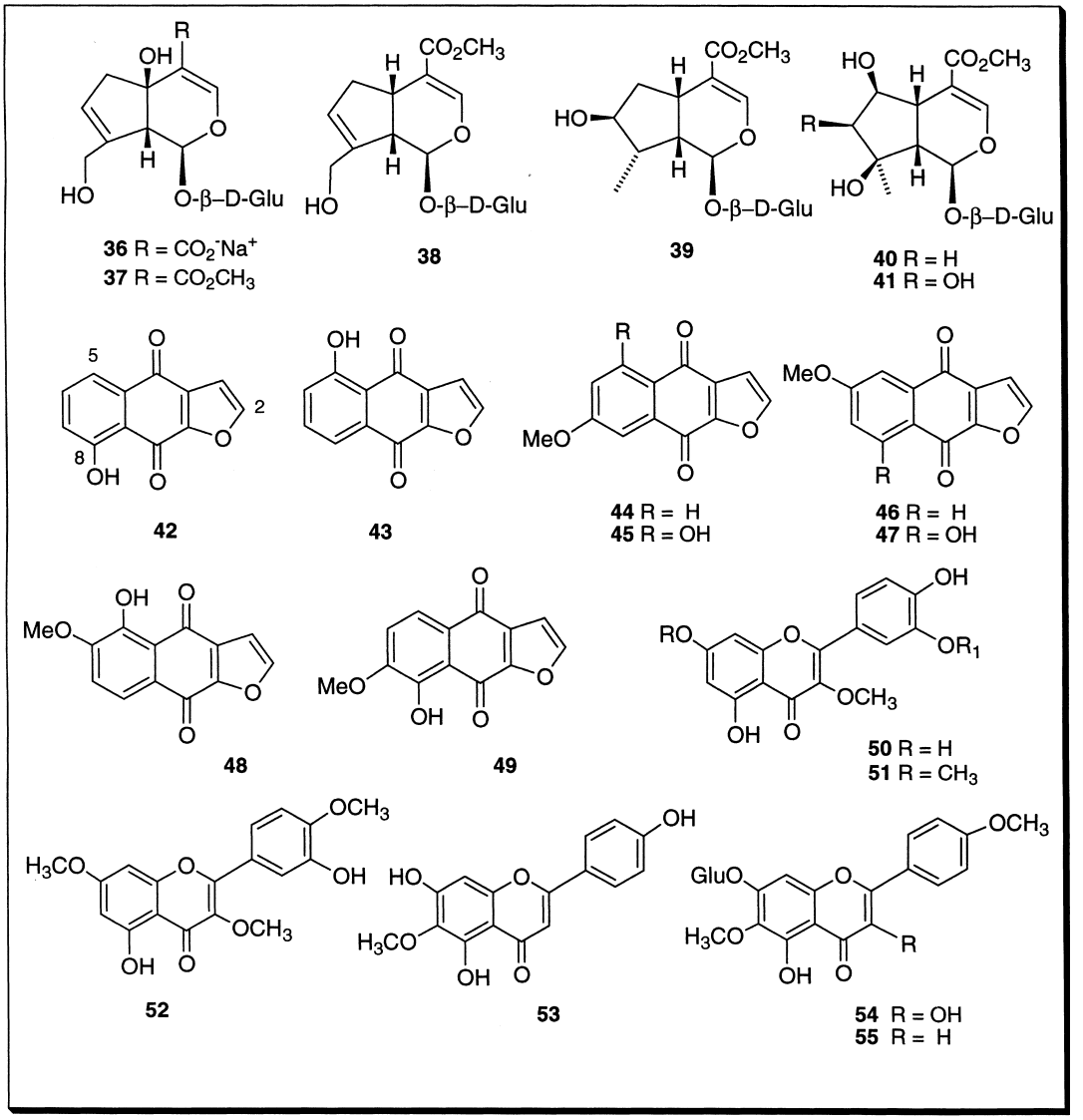


Fig. 3. Ursolic acid, lupane and euphane triterpenes isolated from *L. camara*.

and stems for all three taxa in autumn. As part of a taxonomic study of *Lantana*, greenhouse grown plant were shown to contain the sodium salt of theveside (**36**) in both leaves (800 ppm) and roots (900 ppm), but theviridoside (**37**), the corresponding methyl ester (320 ppm), was only found in the roots [46]. Also from the roots,



geniposide (**38**), the biosynthetic precursor of theveside, has been isolated, together with 8-epiloganin (**39**), shanzhside methyl ester (**40**) and lamiridoside (**41**) [47,48].

3.4. Furanonaphthoquinones

The hexane extract of the roots of a sample of *L. camara* collected in Sri Lanka, contained the quinone diodantunezone (**42**), previously isolated from *L. achyranti-*

folia [49], and its regioisomer (**43**) [50]. The two pairs of inseparable isomers (**44**,**46** and **45**,**47**) were also isolated from this extract, whereas the methanol extract of the roots contained **48** and **49** [50].

3.5. Flavonoids

The acetone wash of the leaves of *L. camara* contained 3-methoxy-, 3,7-dimethoxy- and 3,7,4′-trimethoxyquercetin (**50–52**) [36], whereas hispidulin (**53**) was isolated from the stems [33]. The flavone glycoside camaraside, isolated from the leaves, was originally assigned the wrong structure [51] which was later corrected to **54** [52,53]. It has also been isolated from *L. camara* var. *aculeata* together with pectolinarigenin 7-*O*-β-D-glucoside (**55**) [54].

3.6. Phenyl ethanoid glycosides

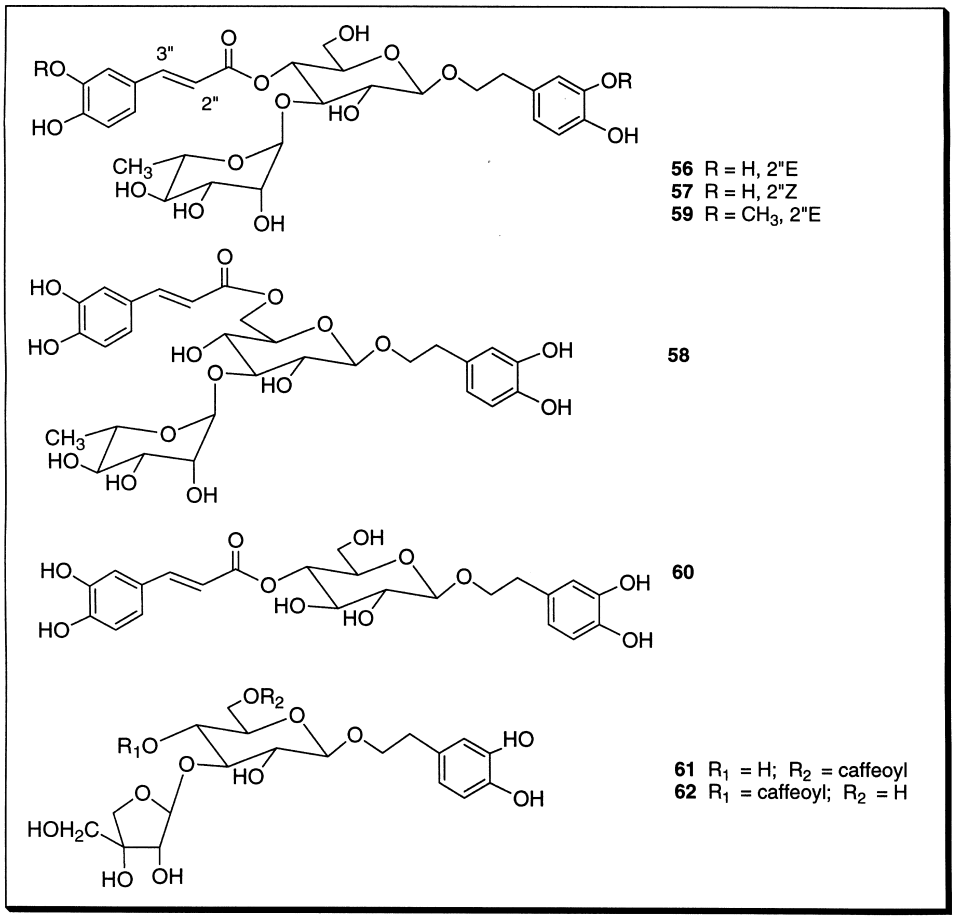
Verbascoside (**56**), a widespread phenylethanoid, has been isolated from *L. camara* [55,56]. The *Z*-isomer of verbascoside (**57**) has also been found to co-occur with verbascoside in *L. camara* var. *aculeata* [54] but it is useful to note that *trans–cis* isomerisation of cinnamoyl esters can occur during manipulation of the sample in the light. Isoverbascoside (**58**), which often co-occurs with verbascoside, martynoside (**59**) [56], derhamnosylverbascoside (**60**), isonuomioside A (**61**) and calceolarioside E (**62**) have been isolated from *L. camara* [57].

3.7. Miscellaneous compounds

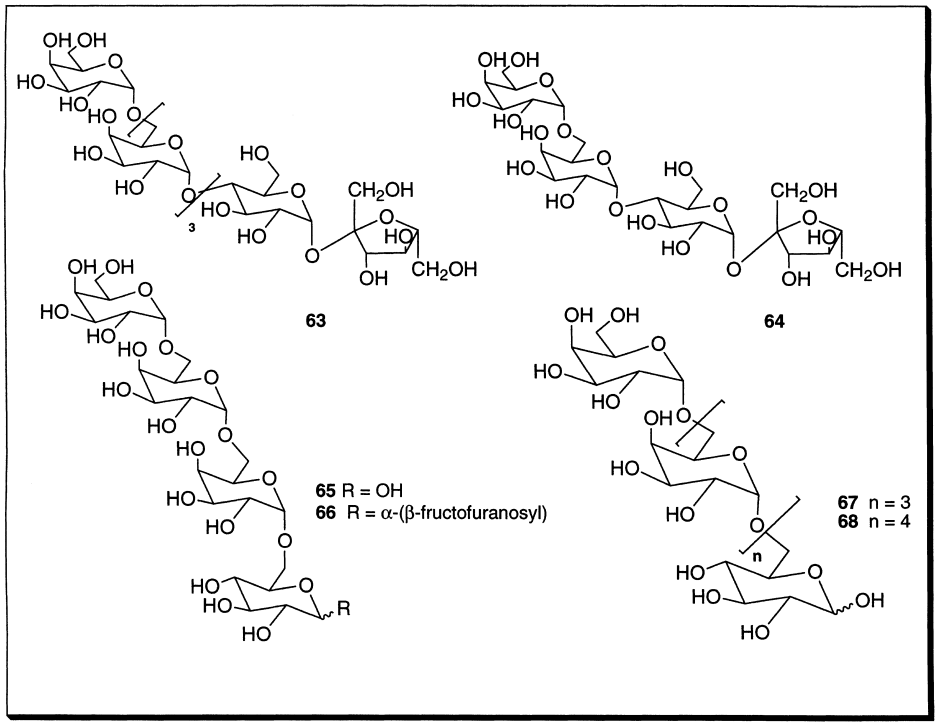
Although a number of members of the Verbenaceae produce diterpenes [58], with the exception of phytol [19], none have so far been isolated from *L. camara.* The typical plant steroids, β-sitosterol, campesterol, stigmasterol as well as β-sitosterol glucoside have been isolated from the stems of *L. camara* [19,33] with β-sitosterol found to be present in consistently high yields [19]. Six oligosaccharides, ajugose (**63**), stachyose (**64**), verbascotetraose (**65**), verbascose (**66**), and lantanose A (**67**) and B (**68**) were isolated from the roots [47].

4. Toxicology

Some taxa of *L. camara* are toxic to ruminants and poisoning has been reported from Australia, India, New Zealand, South Africa and the Americas [2,59,60]. Losses are of particular concern in Australia and India. Of 29 taxa found in Australia, eight have been found to be toxic to livestock [61]. All the toxic taxa contained lantadene A and B and both (80 and 200 mg/kg, respectively) have been shown to be toxic to sheep. The 3β-hydroxy analogue of lantadene A (**9**) is also toxic (40 mg/kg) but, normally, does not occur in sufficient quantity to contribute significantly to the toxicity. The amount estimated to be present in a toxic dose of *Lantana* leaves is 3 mg/kg.



Toxicity is not cumulative and only occurs when sufficient amounts of toxic plants are consumed at one feed, particularly when hungry stock are introduced into a *Lantana*-infested field. Not all species of *L. camara* are toxic, and, of those that are, susceptibility to poisoning varies with different animals. It is generally accepted that lantadenes A, B, D, compound **9** and icterogenic acid (**17**) are toxic to sheep, cattle and goats, but horses, rats, neonatal calves and lambs are not susceptible to lantadene A [60]. Photosensitisation is the most prominent clinical sign of poisoning. Photosensitive dermatitis occurs within 1 or 2 days and as the disease progresses, large areas of skin can become necrotic. Jaundice is prominent within 2–3 days with yellowing of the sclera and other mucous membranes. Loss of appetite in poisoned animals occurs within 1 day and there is a decrease in ruminal motility. The most severely poisoned animals die within 2 days of poisoning, but usually death occurs after 1–3 weeks after poisoning. The pathology of *Lantana*



poisoning has been described [59]. The liver is enlarged and yellow, the gall bladder is grossly distended, and the kidneys are swollen and pale in colour.

It has been shown that only small amounts of ingested toxins are absorbed. The oral toxic dose of lantadene A for sheep is 60 mg/kg, whereas 1–3 mg/kg is toxic by intravenous route [60]. Secondly, continuous absorption of the toxins is necessary for the disease to be maintained. Also, the occurrence of ruminal stasis causes amounts of the toxins to be retained in the rumen. Apparently, incipient liver injury initiates a reflex which slows ruminal motility. The toxins, adsorbed from the rumen and small intestine, are transported to liver by portal blood. They are metabolised in the liver and secreted in bile where they injure bile canalicular membranes thus inhibiting bile secretion. The effects of cholestasis are retention of bilirubin (jaundice), retention of phylloerythrin (photosensitisation) and ruminal stasis which maintains levels of toxins in the rumen and allows progress of liver injury [62].

5. Bioactivity of metabolites

In this section, the biological activities, other than toxicity to ruminants, of the more significant metabolites from *L. camara* are considered.

5.1. Pentacyclic triterpenes

The ursolate acetate **27** was found to be active (30 μg/disk) against *Staphylococcus aureus* and *S. typhi* with an average antimicrobial index of 0.95 and 0.55. By comparison, chloramphenicol for *S. aureus*, and tetracycline for *S. typhi* had an index of 1.6 and 0.8 at the same concentration [26]. Both **15** and **27**, which were isolated from a sample of *L. camara* growing in the Philippines [26], showed high antimutagenic activity in the mouse. At 6.75 mg/kg they reduced the number of micronucleated polychromatic erythrocytes induced by mitomycin C by 76.7% and 60%, respectively.

Lantadenes A–C, and compounds **9** and **10** inhibited Epstein–Barr virus activation in Raja cells induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Compound **10**, lantadene B and C being active even at 10 mol triterpenoid/1 mol TPA, they could be considered valuable inhibitors of tumour promoters in vivo [63]. Lantadenes A and B were shown to have inhibitory effects on the two-stage carcinogenesis of mouse skin papillomas, using 7,12-dimethylbenz[*a*]anthracene as an initiator and TPA as a promoter. Lantadene B (47 μg), applied before each treatment of TPA, delayed the formation of papillomas on mouse skin, reduced the rate of papilloma-bearing mice (by 15% at 20 weeks) and reduced the average number of papillomas/mouse (50% at 20 weeks) [64].

Considerable interest has been shown in the anti-inflammatory action of some triterpenes [65]. For example, oleanolic acid (**8**) and ursolic acid (**22**) have significant activity (IC_{50} 2–4, 6 μM) as inhibitors of human leucocyte elastase (HLE). This enzyme participates in the destruction of elastin and plays a role in chronic disorders such as pulmonary emphysema, cystic fibrosis, hepatitis and rheumatic arthritis.

Inhibitors of cyclooxygenase isoenzyme, COX-2, are of interest since they exhibit anti-inflammatory effects with fewer gastrointestinal side effects compared to non-steroidal anti-inflammatory drugs. Under normal conditions, levels of COX-2 are very low in most cells, but a 10–80-fold increase of COX-2 occurs after induction by cytokines, growth factors, oncogenes, serum and tumour promoters. The increased production of prostaglandins, observed at acute and chronic inflammation sites, is thought to be due in part to up-regulation of COX-2. Ursolic and oleanolic acid possess inhibitory effects on inflammation and on various stages of tumour development [66]. In a recent study, ursolic acid was shown to have COX-2 inhibitory effect with an IC_{50} value of 130 μM and a COX-2/COX-1 selectivity ratio of 0.6. Oleanolic acid showed IC_{50} 295 μM and a ratio of 0.8 [67].

5.2. Tetracyclic triterpenes

Experimental *Lantana* poisoning, by administration of crude lantadene fraction from the leaves, was noted to be accompanied by haematological changes in sheep that indicated an increase in coagulation time and prothrombin time, and a decrease in blood sedimentation rate, total plasma protein and fibrinogen [68]. Thrombin inhibitory activity was found to be associated with the euphane lactone

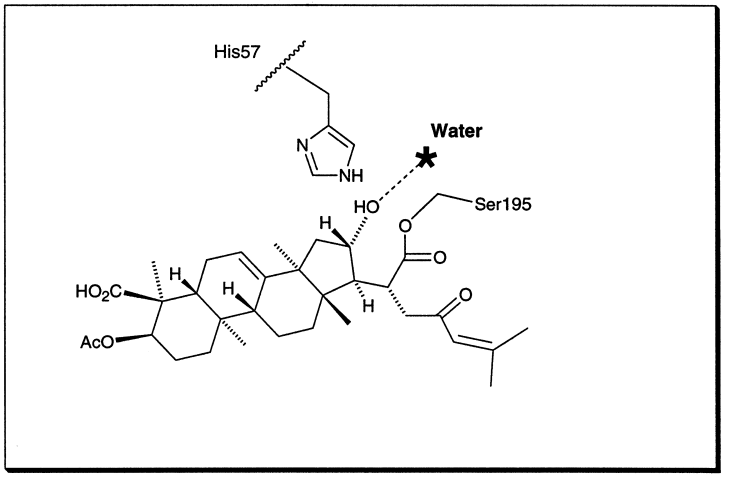


Fig. 4. Schematic of interactions of **32** at the α-thrombin active site.

triterpenes **31–35** [44] which inhibit the blood-clotting cascade via acylation of the active site Ser 195 residue of thrombin. This acylating activity is generic towards other serine proteases [69]. The lactones **31–35** are potent inhibitors of α-thrombin and, to a lesser extent, of α-chymotrypsin and other serine proteases. α-Thrombin is a serine protease that belongs to the trypsin family and has a central role in the hemostatic process, where it displays both coagulant and anticoagulant activities.

Tight-binding reversible competitive inhibition was shown by compounds **32** and **34**. Protease inhibition involves the opening of the lactone ring and acylation of the active-site serine 195. The IC_{50} for α-thrombin, α-chymotrypsin and trypsin was 0.004, 0.07 and 0.07 for **32** and 0.004, 0.01, 0.12 μM for **34**. X-Ray crystallographic studies of the α-thrombin–**32** and α-thrombin–**34** complexes showed the inhibitor in the ring opened form. The hydroxyl group that attacks the seryl ester probably occupies the position normally taken by water during deacylation of peptide substrates. A schematic of the α-thrombin–**32** complex is shown in Fig. 4. Model compounds incorporating [5,5] *trans*-fused indane lactones have been tested as inhibitors of thrombin [70,71]. Although some of these showed significant activity as HLE, chymotrypsin and human α-thrombin inhibitors, they were relatively unstable in plasma [70,71]. Model compounds containing a lactam had much enhanced plasma stability compared to their lactone counterparts and showed appreciable in vitro anticoagulant activity [72].

5.3. Iridoid glycosides

This class of compounds is well represented in plants used in folk medicine for the preparation of bitter tonics, sedatives, febrifuges, cough medicines, remedies for wounds and hypotensives [73]. Individual compounds are known to exhibit

various pharmacological activities including cardiovascular, antihepatotoxic, choleretic, hypoglycemic, anti-inflammatory, antispasmolytic, antitumour and antiviral activity [73]. Of the iridoids so far isolated from *L. camara*, only geniposide (**38**) has been studied in detail. Geniposide inhibited hepatoxicity and the DNA repair synthesis induced by aflatoxin B1 in rat primary hepatocytes. The possible mechanism involves enhancement of levels of glutathione *S*-transferase and GSH peroxidase [74,75]. Intraduodenal administration of geniposide showed a delayed but potent choleretic action in rats. It was observed that the aglycone, genipin, is the active agent since geniposide had no effect on intraportal administration [76]. Iridoid glycosides are known to be hydrolysed in the gastrointestinal tract. In mice, geniposide (**38**) was metabolised to the aglycone genipin which was found in all of the gastrointestinal tract especially the cecum and the colon [77]. Geniposide is hydrolysed by β-D-glucosidases from intestinal bacteria [78,79]. Genipin (50–100 mg/kg) exhibited bile acid-independent choleretic action. Injected into the mesenteric vein of rats, genipin markedly increased the bile flow. Interestingly, this effect might counteract that shown by the lantadenes. Geniposide (**38**) and genipin showed hypolipidemic activity in hyperlipidemic rats [80]. It was also found that geniposide showed cAMP phosphodiesterase inhibitory activity [81].

5.4. Furanonaphthoquinones

Recent interest in these compounds arises from their pronounced cytotoxicity to a range of tumour cell lines. Studies on structural activity relationships revealed that activity is enhanced by an alkyl group at position 2 and a hydroxyl group at positions 5 or 8 [82]. Diodantunezone (**42**) was tested for cytotoxicity against KB epidermoid nasopharynx, K562 human leukaemia and P388 lymphocytic leukaemia cell lines and found to be active (IC_{50} 6.76, 9.2 and 7.94 μmol/l, respectively). The corresponding methyl ether showed greater activity (IC_{50} 1.3, 1.32 and 1.86 μmol/l, respectively) [83]. A number of furanonaphthoquinones have been shown to possess antimicrobial activity against Gram-positive bacteria and fungi [84], inhibitory effects on the Japanese encephalitis virus [85] and pronounced activity against *Trypanosoma* parasites [86]

5.5. Phenylethanoid glycosides

Verbascoside (syn: acteoside, kusaginin) is represented in several plant families [87] and has been shown to display an interesting spectrum of biological activity. It is an inhibitor of PKC (protein kinase C), the Ca^{2+}/phospholipid dependent protein kinase that plays a crucial role in signal transduction, cell proliferation and differentiation [55]. Verbascoside inhibited PKC in a concentration-dependent manner and showed an IC_{50} of 25 μM. The inhibitory effect could be overcome by addition of extra ATP, indicating that the interaction with the compound was reversible [55]. A more recent study reports IC_{50} 9.3 μM [88]. Verbascoside also inhibited rabbit lens aldolase reductase [89] and lipid peroxidation [90]. It exhibited immunomodulating activity [91] and immunosuppressive properties [92] and appar-

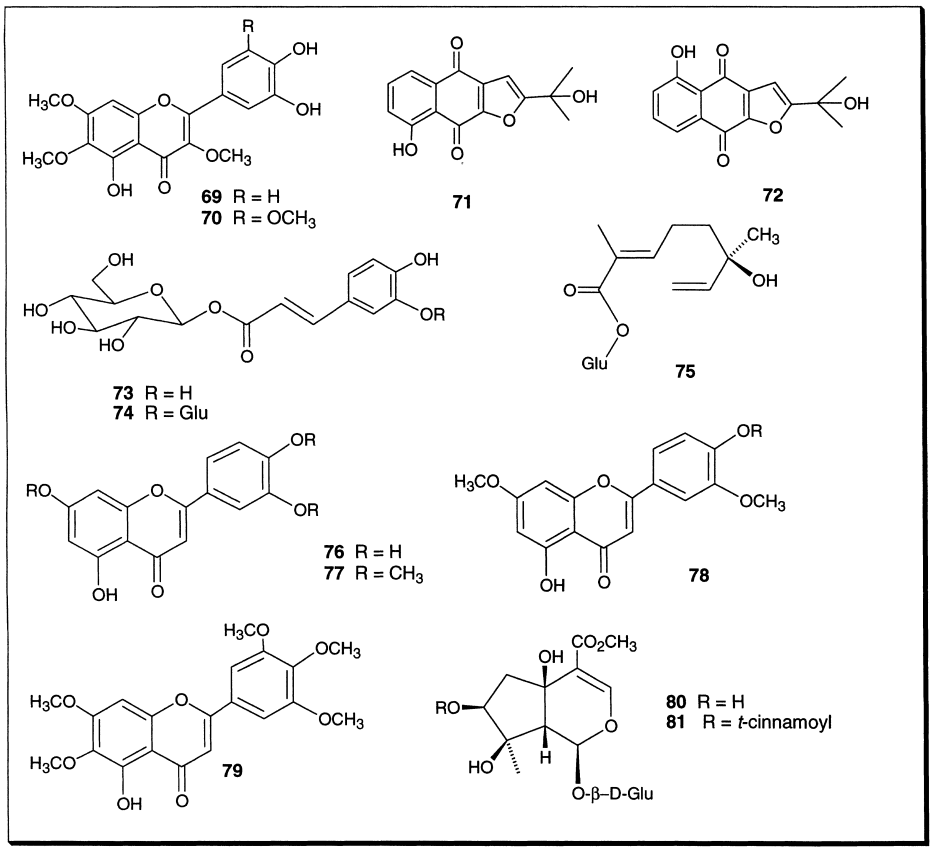
ently potentiated the anti-tremor effect of L-DOPA [93]. It displayed in vivo activity against murine P-388 lymphocytic leukaemia (ED_{50} 2.6 μg/ml compared to isoverbascoside ED_{50} 10 μg/ml) [94], antiproliferative effect in vitro against L-1210 cells (IC_{50} 13 μM) [55], analgesic activity [93,95], protection against oxidative haemolysis [96], antibacterial activity (*E. coli*) and was active against the Aujeszky virus [91]. Verbascoside is a potent cardiotonic and vasodilatory agent and has potential as an antihypertensive agent [97,98]. It markedly increased levels of cAMP and of prostacyclin [99,100]. The dimethoxy derivative, martynoside (**59**), had similar activity and increased (16%) chronotropism and coronary perfusion rate (44%) in the Langendorff isolated rat heart [57].

Respiratory syncytial virus (RSV) is a cause of lower respiratory tract infection in infants and young children [101]. Some infants with RSV lung infection cough excessively giving symptoms resembling whooping cough. Verbascoside (antiviral activity, EC_{50} 0.80 μg/ml; cytotoxicity, IC_{50} 76.9 μg/ml; selective index, SI 85.4) and isoverbascoside (EC_{50} 0.0.62 μg/ml; IC_{50} 51.4 μg/ml; SI 84) exhibited activity against RSV and in vitro these compounds had better antiviral activity than ribavirin (EC_{50} 1.8 μg/ml; IC_{50} 35 μg/ml; SI 19), an approved drug for treatment of RSV infections in humans. Overall, RSV inhibition requires two catechol groups and a central sugar unit [101,102].

6. Phytochemistry of other *Lantana* species

The phytochemistry of other *Lantana* species has received much less attention and a summary of the work carried out is given below.

From the aerial parts of *L. achyrantifolia* Desf., the flavones penduletin (**69**) and chrysosplenetin (**70**) were isolated, whereas the naphthofuranoquinone diodantunezone (**42**) was isolated from the roots [49]. The presence of the corresponding methyl ether was suggested, but the compound was not isolated. Closer scrutiny of the quinone showed that it was a mixture of the isomers (**42**, **43**) and that it co-occurred with two other compounds (**71**, **72**) [50]. From the extracts of *L. hybrida*, 1-(3-glucosyloxy-4-hydroxycinnamyl)glucose (**73**) [103] was isolated, whereas 1-caffeoylrhamnose (**74**) was obtained from the flowers [104]. *Lantana indica* Roxb. is a shrub native to India where it has been used as a sudorific, intestinal antiseptic, diaphoretic and in the treatment of tetanus, rheumatism and malaria in the Ayurvedic system of medicine [105]. The essential oil contained 56 compounds of which 46 were terpenes. Carvomenthone, linalool, camphor, borneol, terpin-4-ol, α-terpineol, methyl heptanoate and propyl butanoate contributed to the pleasant smell [106]. The sterol fraction of the leaves of *L. indica* contained β-sitosterol (81%) and cholesterol (8%) [107]. The leaves also contained a mixture of C_{23}–C_{33} alkanes, the major components being the C_{29}, C_{31} and C_{33} alkanes, and C_{28}–C_{30} alcohols [108]. From the roots, oleanolic acid, ursolic acid, 3β-24-dihydroxyolean-12-en-28-oic acid [109] and 24-formyl-3-oxoolean-12-en-28-oic acid [105] were isolated. 24-Hydroxy-3-oxooleanolic acid and methyl-24-hydroxy-3-oxoursolate have also been identified in *L. indica* [110].



The monoterpene glucoside ester **75** and verbascoside (**56**) have been isolated from the leaves of *L. lilacia* Desf., preparations from which have been used in the treatment of bronchitis [111].

Lantana montevidensis (Spreng.) Briq. is a species closely related to *L. indica* [1]. The leaf exudate of *L. montevidensis* has been shown to contain luteolin (**76**) and its 3′,7-dimethoxy- (**77**) and 3′,4′,7′-trimethoxyderivatives (**78**) [37]. A crystalline carotenoid has been detected in this variety, as well as in several taxa of *L. camara*, but its structure was not determined [19]. Interestingly, *L. montevidensis* contains no lantadene A or B or any significant amounts of triterpenes [19]. The essential oil of *L. orangemene* was obtained in 0.2% yield and was shown to consist primarily of monoterpenes [112,113].

Comparative studies on the composition of the essential oils of *L. salvifolia* Jacq. collected at different altitudes in Ethiopia has revealed that samples collected at lower altitude (1600 m) provided more oil, whereas those from higher altitude (3500 m) were richer in more oxygenated components [114].

Lantana trifolia L. is a species used in the folk medicine of Rwanda [115]. The major components in the essential oil were found to be germacrene D and caryophyllene [116]. The pentamethoxyflavone, umuhengerin (**79**), isolated from the leaves, has shown weak antibacterial and antifungal activity (at 200 μg/ml) [115]. No iridoid glycoside were detected in this species [46].

Lantana tiliaefolia Cham. is the most common *Lantana* in Brazil, but it is not considered a weed because it is controlled by a complex of natural predators such as insects and fungi [117]. Unlike *L. camara*, the leaves and stems did not contain lantadene A or B or lupanes and the content of ursane derivatives was higher. In all, ursonic, ursolic, oleanolic, oleanonic, 24-hydroxy-3-oxo-olean-12-en-28-oic acid and 24-hydroxy-3-oxo-urs-12-en-28-oic were isolated [117]. The iridoid glycosides, lamiide (**80**) (45 ppm) and durantoside (**81**) (10 ppm), were detected in the roots of *L. viburnoides* (Forsk.) Vahl [46].

7. Concluding remarks

Despite its popularity as an ornamental plant, it is clear that a number of taxa of *L. camara* are aggressive weeds and some pose problem to ruminants feeding on them. Attempts to control *L. camara* using mechanical, chemical and biological means have met with limited success [2,6] and it appears that an integrated approach is required. Given that there are large areas infested with this plant, it is reasonable to consider if large scale use could be made of its biomass. For example, liquid CO_2 extraction of the leaves provides reasonable amounts ($\sim 2\%$) of essential oil and the roots are considered to be a good source of oleanolic acid [37]. The iridoid theveside comprises 6% of the dry weight of the stem of the red flowering taxa harvested in spring [45] and verbascoside (**56**) can be obtained in 2% yield from the leaves and branchlets. The triterpene fraction containing the toxic lantadenes can readily be separated from the more polar components, the phenylethanoids and iridoid glycosides, by solvent fractionation. Other biological activities attributed to various extracts of *L. camara* warrant further investigation. Extracts from the flowers have been shown to have a repellent effect on *Aedes* mosquitoes [118], extracts from the leaves exhibited insecticidal and allelopathic action [2] and the essential oil of some taxa demonstrated juvenile hormone activity [2,119]. The presence of alkaloids in *L. camara* has been indicated [2,120], but none have been identified so far.

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