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Review Article

A Comprehensive Review of Historical and Ethnobotanical Aspects, Chemical Constituents and Biological Activities of *Euphorbia umbellata* (Pax) Bruyns

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ABSTRACT

Euphorbia umbellata (Pax) Bruyns (*Synadenium grantii* Hook.f.) is an African shrubby tree that has a long use in traditional human and veterinary medicine. Nowadays in Brazil, its latex has been extensively used to treat arthritis and several types of cancer, among other health disorders. This study comprehensively reviewed data reported on history and ethnopharmacological aspects of *E. umbellata*, as well its chemistry and preclinical pharmacology. The Web of Science, SciFinder, Google Scholar and the Prelude Medicinal Plants database were prospected by using the three precedent botanic synonymous for the species. The resulting assembly was complemented by searching available online monographs, and physical and online books on the theme. The compiled information was organized according to each specific survey. Thirty-three distinct popular uses and approximately forty recipes were found for the latex and leaves. Oral and topical administrations of latex or leaves were predominant in human cases. Veterinary uses mostly targeted antiparasitic and anti-inflammatory therapy, and topical application of latex stood out. Prospection of the experimental studies led to twenty-four entries for biological activities *in vitro*, mainly related to anticancer investigations. Thirty-five compounds comprising triterpenes, diterpenes and phenolics, besides typical proteases, have been characterized in the species. Traditional usage of *E. umbellata* may be correlated with results on the cytotoxicity, antiviral, and anti-ulcer ability of extracts from diverse parts of the plant. To date, the most significant experimental progress has been related to *E. umbellata* terpenoidal metabolites.

Keywords: Ethnomedicine, *Euphorbia umbellata*, Phorbol esters, *Synadenium grantii*, *Synadenium umbellatum*, Triterpenes.

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INTRODUCTION

Standing among the most diverse and prominent groups in Angiosperms, the family Euphorbiaceae Juss. comprises 220 genera. *Euphorbia* L. is the most populous genus in the family, comprising 2046 species,[1] which are notable for the production of a whitish latex, usually endowed with irritating properties related to plant defense against insects and herbivores.[2,3] On dispersing its species from tropical African and American origins, the genus *Euphorbia* reached a cosmopolitan occurrence and acquired an extreme phenotypic plasticity[4] as a way to adapt themselves to the most diverse habitats, such as forests and deserts.[5] They are therefore found as small globose and succulent individuals to shrubs, bushy and large trees. In arid regions, they can assume the cactiform morphotype.[6] The taxonomic difficulty with many species of *Euphorbia*, due to the extremely diverse and complex set of morphological parameters, has been historically reported.[7] The high variability in size and diversity of species has induced a series of studies on the phylogeny of *Euphorbia* and related genera, as revised elsewhere.[6-8]

The species in focus, *Euphorbia umbellata* (Pax) Bruyns is native to Tanzania,[9,10] although some botanical registers broaden this cradle to include the area from South Sudan to Burundi.[11] From the East Africa region, it initially spread to surrounding countries to later reach India. It is a grayish-bark shrub that, under normal circumstances, grows up to just over 3 meters, but exceptionally can reach 10 m in height, with many branches from the base. The diameter of the main stem varies from 12 to 15 cm. The young branches, 1-2 cm in diameter, are tender, sometimes fleshy and woody green when old. The plant has alternate, sessile, fleshy and thin leaves, obovate and obtuse at the apex, with short tip, low tapering, whole or serrated, glabrous or rarely hairy, with a boat shape along the central rib, slightly green, 7-17 × 2.5-6 cm.[10,11] The petiole is short; the leaves are sequentially closed, sometimes dyed red, with flowers in the form of dark red curls. The plant

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contains abundant white latex and grows quickly to result in bulky shrubs.[10] For this reason, it was commonly used in Kenya and India to compose hedges,[12] in addition to serving as an ornamental.

Historical highlights

The genus *Euphorbia* L. owes its name to King Juba II of Mauritania (25 BC), who used a remedy produced from the latex of a succulent plant and, given its astonishing curative power, named it suggestively *Euphorbium* in honor of his Roman physician, Euphorbius, who was equally burly (Euphorbio = well-nourished in ancient Greek).[13] Euphorbium was obtained from the plant latex and was much later classified as *Euphorbia resinifera*. Its active ingredient, resiniferatoxin, is highly active in relieving neuropathic pain caused by diabetes, and its chemical structure, elucidated in 1975, has been proven to act analogously to capsaicin. The study of the mechanism of action of resiniferatoxin was responsible for an exceptional advance in the knowledge about the role of vanilloid receptors in nociception.[14]

At the time of the appearance of *euphorbium*, the denomination of Euphorbia for the plant rivaled the term *tithymales*. Both records cohabited in *Dioscorides' De Materia Medica* (30-90 AD); the second term has been used since Hippocrates (470-370 BC) to designate related species growing around the Mediterranean region. Its origin is the antique word *tithymalos*, inspired by *titthòs* (udder) and *malos* (pernicious). Maintained by scientists and doctors of that time, such as the Greek Teofrasto and the Latin Plinio the Old, and lasting long enough to coinage numerous Mediterranean species, the name *Tithymalus* for the genus was only abandoned after the classification by Linneu, which rescued and consolidated the term *Euphorbia* in 1753.[15] However, it is certain that, apart from the fusion of data recorded by the luminaries of that time and some legendary facts, the name *Euphorbia* for the genus was primarily inspired by the medicinal properties of the latexes released by the species it comprehends.

The toxic property of latexes of species that would later be pooled in the genus *Euphorbia* by Lineu appeared already in the ancient Greco-Roman records. When referring to a medicinal species of this genus in *De Materia Medica*, Dioscoride mentioned, "when a person harvests his latex, he must not face the wind, nor touch his eyes with his hands, and first he must cover his skin with grease and wine". In his work *Epidemics*, Hippocrates reports two cases of *tithymale* poisoning (Hippocratic Treaties; T.5). Paradoxically, these and other Western authors are also emphatic in recognizing the excellent medicine represented by latex, endowed with emetic and purgative properties, in addition to being caustic, in right measure, to soften calluses and eliminate warts.[15,16]

One of the most emblematic species of the family is *Euphorbia lathyris*, which already appeared in the European pharmacopoeia under the French name "epurger" (purgative, depletive) due to its indication to eliminate catarrh and other bilious humors. This vernacular was later anglicized to "spurge" and forth established to designate the latex-producing species of the Euphorbiaceae family in general.[15,17]

Euphorbia umbellata (*Synadenium grantii*) first collection and determination

The finding of the African species *Euphorbia umbellata* by the occidental man is surrounded by a peculiar history that dates to the expedition commanded by the British Indian army officer John Hanning Speke in 1860, in which travel he sought to confirm geographic data to corroborate his proposition of Lake Victoria as the outsource of the Nile River. In such an enterprise, he was accompanied by the Scottish Captain (lieutenant-colonel) James August Grant, a school-educated man and enthusiastic adept of Natural Sciences.[18] Throughout the course of the mission, Grant collected copious and varied biological material, in which 831 plants stood out,[19] in addition to acting as a draughtsman depicting a subtle but broad register of the lifestyle of the communities where they settled during the trip.[20] The collected plants were exsiccated and, following a harsh itinerant ground transportation, shipped to London to be delivered at the Royal Herbarium at Kew.[19] The list of plants Grant collected was organized by the botanist Thomas Thomson and published in the Appendix to Speke's Journal of the Discovery of the Source of the Nile. Approximately one hundred of them had their images reconstituted from the very exsiccate in stunning, true-to-the-original images by the talented artist aggregated to Kew Gardens, Walter Hood Fitch.[21,22] The keepership of the herbarium was then Professor Daniel Oliver, who began his work at Kew in 1858 after being invited by the director Sir William Hooker, especially to support his son, Joseph Dalton Hooker, in the task of organizing and distributing the voluminous material accumulated by the expeditions to the East Indies.[23] When the plants collected in Africa arrived, J. D. Hooker was about to succeed his father in the direction of the Royal Botanic Gardens, Kew, which he did in 1865.

Among the non-flowered exsiccates, one Euphorbiaceae specimen caught the attention of Thomson, who observed that it still had some latent freshness in its branches. Grant's notes on this plant were very succinct and restricted to "a bushy tree of 10 to 25 feet, with small red flowers. Milk falls in drops when any part of the tree is broken", occurring on the outskirts of the villages and having been collected in February 1862, at the latitude recorded by him as 30° 15' N. After Thomson commenting on this observation with J. D. Hooker, they decided to proceed to planting the stem cuttings. This proved successful as the plant grew up well and flowered in the Royal Gardens, Kew, in November 1866.

Such a development allowed Hooker to classify the specimen thereafter as belonging to the 'curious' genus *Synadenium* with a basis in descriptions of two pioneer species from Natal, South Africa (*S. arborescens*) and Madagascar (*S. carinatum*);[24] the plant collected by Grant was closely allied to the former. Both had been described by the botanist and explorer Swiss Pierre

Edmond Boissier, thus establishing the genus *Synadenium* Boiss. in his monograph on Euphorbia published in the fifteenth volume of De Candolle's Prodromus. Hooker then made a more complete description of the species and called it *Synadenium grantii* Hook. f., certainly converging with the suggestion of Daniel Oliver (to whom Hooker dedicated the volume wherein his first botanical description appears)[24] to honoring Captain Grant and his fabulous efforts. Due to its ornamental appeal, *Synadenium grantii* Hook. f. was spread in England from 1867 through cultivation in greenhouses.[25]

In 1895, the German botanist Ferdinand Albin Pax described *Synadenium umbellatum* as a new species based on morphological differences he found in comparison with *S. grantii* – although both sprouted the branches identically – as well as with *S. piscatorium*, a known fish poison at that time. The same publication brings along the description of var. *puberulum*, also determined on a morphology basis. Both samples were collected originating in distinct locales in the Mozambique District, at that time part of the German East Africa.[26,27]

In the first decade of the 21st, phylogenetic DNA-based studies conducted by the South African botanist P. V. Bruyns on a plethora of species native to the African continent led to rearranging the taxonomic relationship among several closely *Euphorbiaceae* genera.[28] In the Bruyn's studies, a range of species of distinct genera were included in the Euphorbia taxon, as was the particularly relevant case of species belonging to the *Synadenium* genus. In this context, the binomials *Synadenium grantii* Hooker f. (1867), *Synadenium umbellatum* Pax (1894); *Synadenium umbellatum* Pax var. *puberulum* N.E. Brown (1911) were aggregated to *Euphorbia umbellata* (Pax) Bruyns[11] as the one that endures today. In addition, it might be noteworthy that Bruyns considered nesting the species *Euphorbia pseudograntii* Bruyns into the *E. umbellata* domain. However, this was quite transient,[29] as the same binomial had already been used by Ferdinand Pax to determine a discrete species that, except for the bisexual cyathium inflorescence,[30] showed enough similarity with the *Euphorbia grantii* formerly described by Oliver.[21] It is currently accepted by the name *Euphorbia grantii* Pax, despite the suggestion elsewhere of belonging to *Euphorbia kirkii* (N.E.Br.) Bruyns (formerly *Synadenium kirkii* N.E.Br.).[29] Since Bruyns' species repositioning is relatively recent, the informational and scientific background of *Euphorbia umbellata* remains primarily upon the studies described under previous synonyms, always referring to the *Synadenium* genus. Thus, the term *Synadenium grantii* is absolute in ethnobotanical registers and largely prevalent in multidisciplinary studies, even after Bruyn's review.

Ethnobotanical and traditional uses

At first, all species in East Africa reported as *Synadenium* were recognized as fish poisons, as they are highly toxic to cold-blooded animals.[10] However, Neuwinger (2004) later listed only five species of this genus as poisons for this purpose.[31] There are diffuse reports, such as those of the Belgian botanist Dewevre, who collected a species used in ordeal rituals in Zaire in 1895. In the Bolobo region, on the banks of the Congo River, people accused of theft received a drop of latex in their eyes, and if this caused them to lose their eyesight, they were found guilty; nothing happening, the indictment would be cleared. The vernaculars recorded by Dewevre were *Kessongini* (Kasongo area, Lualaba River), *malua* (lake Tanganika), *magueli* (Kwango River) and *mokolisi* (Boussira, Guinea), but only the generic level was ensured for the plant used in the ritual as being *Synadenium*.[10]

The known toxicity of some *Synadenium* species led them to integrate poisonous mixtures in which Ugandan natives usually soaked their arrows.[32] This tradition seems to have inspired the Kikuyus, an ethnic group from Kenya, during the Mau-Mau revolt to furtively poison the cattle raised by the colonists in the lands from which they had been expelled during the process that marked the country's decolonization.[33] The latex of species classified in the *Synadenium* genus has often been described as skin irritant and causative of blindness.[17] In 1938, the botanist Bally considered *Synadenium ballyi* Werderm to be a 'scary poison', as its latex was also used to poison monkeys.[10]

From Kew, the plant was distributed to other parts of Europe and the Americas. It arrived in Brazil by the hands of travelers at the end of the 20th century, entering then to Peru and other South American countries via the Amazon River, already associated with the belief in curing cancer.[34] However, shortly after it arrived in the new countries, the intense local reactions in livestock and eventually in humans, caused by contact with the latex, led the species to be officially considered in the scope of dermatitis-inducing plants[35] and soon classified as toxic.[9] This species is recognized as a pluripotent medicinal plant in Brazil[34] and Peru,[36] although it is warned to be toxic by medicinal plant sellers.[37] Despite such a reputation, it is interesting to note that, unlike other species of *Euphorbia*,[38] reports in the western world are rare and incomplete for the toxic effect of *E. umbellata* latex on humans. In part, this is probably because reports of skin and mucous membrane irritations, being transient and relatively predictable, were not ground for detailed clinical descriptions.[9] Human accidents have been reported in two iconic cases involving a 21-year-old gardener in London[39] and a 5-month-old baby in Colorado.[25] The first case was confirmed with a latex test on a volunteer's forearm; the second showed symptoms that disappeared after 24 to 48 hr, even though they involved the administration of innocuous anti-emetic and anti-allergic medications. The relationship between the skin irritating property of *Euphobia* species (and related genera) and particular chemical constituents has been the subject of many academic studies,[40] also boosting pharmacological studies on this phenomenon.[41]

Data Collection

The Web of Science, SciFinder, Google Scholar, and the Prelude Medicinal Plants database were searched using the

three synonyms by which the species has been reported in the literature. In the latter cited database, although a secondary link is eventually available to access the primary sources, as a general rule, the retrieved documents are not included in the DOI (Digital Object Identifier) system. Other sources included physical books on the medicinal plants' theme as well as books, monographs and symposium notes available online. The compiled information was organized in tables ruled by each specific survey, which concern the building of Table 1 (medico-ethnobotanical), Tables 2-4 (chemical constituents) and Table 5 (experimental studies). Microsoft Excel was used to build demonstrative charts from the tabulated ethnobotanical data.

Table 1: Medico-ethnobotanical uses of *Syndenium grantii Hook* f. (syn. *Euphorbia umbellata* (Pax) Bruyns).

Symptom	Recipe	Vernacular name	Community/country	Refs.
Human Use				
Aborption	Drops in milk of water-decocted leaves, VO	Umukoni (Kirundi)	Zaire-Nil ridge region, Burundi (CA)	[42]
Arthritis	Powdered leaves applied on swallow joints and scarifications	Fangafa (Luo, Kenya)	Kenya (EA)	[43]
Backache, lumbago	Powdered leaves locally applied			
Bronchial asthma	'Total extract' singular or in combination with. *Microglossa pyrifolia* (observational study).	Not mentioned (secondary register)	Different communities, Kenya (EA)	[44]
Cancer	Not specified	Leiterinha, gota-milagrosa (Portuguese)	Juruena Region, Mato Grosso, Brazil	[45]
Cholera				
Cleanser				
Constipation	latex spread on pieces of 4 bananas, dry, smoked, grilled + 2 L milk, VO	Umukoni	South-Kivu, Democratic Rep. of Congo (WA)	[45,46]
Cough	Daily lick of powdered young stems with salt spread on the soil	Umukoni (Kinyarwanda), Bihwiri (Mashi dialect)	Rwanda (CA), Democratic Rep. of Congo (CA)	[47,49]
Fever (unprecise)	Roots, leaves, not specified	Not registered	Nigeria (WA)	[48]
Gastrointestinal and hepatic disorders	#Not specified	Leiterinha, gota-milagrosa (Portuguese)	Juruena Region, Mato Grosso, Brazil	[45]
Impetigo (Inkinamubiri)	External use of leaves composed with Brillantaisia cicatricosa powder in oil, concomitant with decoction of a mix of six other species [a], VO	Umwambutsa	Gisenyi District Rwanda (CA)	[50]
Inflammation of the fingers or toes	Latex applied on inflammation	Nandele	Bulamogi country, Uganda (EA)	[51]
Intestinal parasitism eventually combined with constipation	latex with fresh milk (for children)	Umukoni (Kinyarwanda)	Rwanda (CA)	[46,49]
	Liquid from leaves rubbed in water after passing through fire flames, VO	Umukoni	South-Kivu, Democratic Rep. of Congo (WA)	[46]
	Leaves, latex softened by fire-heating, VO	Umukoni (Kirundi)	Zaire-Nil ridge region, Burundi (CA)	[42]
	Enema with juice extracted from leaves, stems, roots preparation from the bark (mixed or not), age-adapted dosis	Umurerabana (Kirundi)	Burundi (CA)	[52]
Leprosy	roots, leaves, not specified	Not registered	Nigeria (WA)	[48]

continued...

Table 1: Cont'd.

Symptom	Recipe	Vernacular name	Community/country	Refs.
Mumps, otitis ear infections	Roots, leaves, not specified	Not registered	Nigeria (WA)	[48]
	Leaves softened by the heat of fire; two drops of juice in ears	Bihwiri (Mashi dialect)	Kisangani, Democratic Rep. of Congo (CA)	[47,53]
Poison antidote, detoxicant, vomitive in rituals (uburozil)	Hot preparation with two other species [c] (leaves), VO	Umwambutsa	Gisenyi District Rwanda (CA)	[50]
Psoriasis (amahumane y'amabara)	External use of pomade from ashes composed with *Acanthus pubescens*, complemented with leaves decoction together with three other mixed species [b], VO (1/2 glass daily; 1 soupspoon for children)			
Purgative, laxative carminative	Enema with juice extracted from leaves, stems, roots preparation from the bark (mixed or not), age-adapted dosis	Umurerabana (Kirundi)	Burundi (CA)	[52]
Rheumatism (rubagimpande, imijaganyuro)	Leaves prepared with those from 5 other species [d] (not specified recipe)	Umwambutsa	Gisenyi District Rwanda (CA)	[50]
Rhino-pharyngitis	Defoliated stem as a belt around the neck	Not registered	Rwanda (CA)	[54]
Ritualistic, illness as the fact of a magic charm	Not specified. Bad luck (amabuye, ibihago), sensation of strange objects in the body, except the head; leaves pressed in water, VO	Umukoni (Kirundi)	Burundi (occidental) (CA)	[55]
Skin boils, whitlow	Local friction with heat-on-fire softened leaves	Potenge (Tetela), pote (Swahili)	Democratic Rep. of Congo (WA)	[56]
Sore throat	Leaves and ashes, VO	Fangafa (Luo, Kenya)	Kenya (EA)	[57]
Stimulant of child-birth delivery	Decoction of stems, VO, used also after parturition	Engorbobi (Maasai)	Simanjiro country, Tanzania (EA)	[58]
Syphilis	Juice extracted from leaves passed on fire flames, VO	Umurerabana (Kirundi)	Burundi (CA)	[52]
Taenia	Latex (VO)	Umukoni (Kirundi)	Zaire-Nil ridge region, Burundi (CA)	[42]
Thrombosis, heart disorder	Juice from grinded leaves, VO	Not registered	Kisangani, Democratic Rep. of Congo (CA)	[53]
Tuberculosis	Burned leaves mixed with ashes of three other species [e], VO	Umukoni (Kirundi)	Burundi (occidental) (CA)	[55]
Warts, skin callosity	Warm latex from broken stem	Umukoni (Kinyarwanda)	Rwanda (CA)	[49]
	Latex from the leaf	Bihwiri (Mashi dialect)	Democratic Rep. of Congo (CA)	[47]
	#Not specified	Leiterinha, gota-milagrosa (Portuguese)	Juruena Region, Mato Grosso, Brazil	[45]
Whitlow	#Not specified			
Wound	Leaf poder, local application	Umukoni (Kirundi)	Zaire-Nil ridge region, Burundi (CA)	[42]
	Fresh latex (leaves and stems) applied on fresh decoration marks cut on the surface of women's abdomen; swelling indicates healing	Fangafa, ofangafa (Luo)	Kenya (EA)	[57]

continued...

Table 1: Cont'd.

Symptom	Recipe	Vernacular name	Community/country	Refs.
Yaws	Paste of juice from grilled leaves with coal powder	Umukoni (Kinyarwanda)	Rwanda (CA)	[49]
Veterinary Use				
Afterbirth placenta retention	Cattle: Latex or bark decoction	Orkorbobi (Maasai)	Simanjiro country, Tanzania (EA)	[58]
Antiseptic, wound healing in carbuncles	Cattle: Latex on swellings and boils to extract the pus	Fangafa (Luo, Kenya)	Kenya (EA)	[57]
Blackleg (blackquarter), anthrax	Cattle: Roots prepared with equivalent amount (1/4) of roots and bark from two other species [f] + manguyangel, decoction 1 L water 30', filter, cool: 300 mL, adult 3x/day during 3 days, continued by 1/2 doses, VO (b) Sheep: roots prepared with equivalent amount (1/4) of roots and bark from two other species [g], decoction 1 L water 30', filter, tepid: 200 mL, VO	Masheget (Kipsigis)	Kipsigis, Kenya (EA)	[59]
	Cattle: Not specified	Umukoni	Rwanda (CA)	[60]
	Cattle: Milky latex applied on the skin of the limping leg for treatment of blackquarter.	Mdleve (Tsonga)	South Africa (Tsonga)	[61,62*]
External parasitism	Cattle: Leaves, extracted juice diluted in water, VO (reserved for specialists)	Umukoni (Kirundi)	Zaire-Nil ridge region, Burundi (CA)	[63]
Eye microbial infection	Cattle: Sap from squeezed branches topically applied on the "nerve area" (between the eye and the ear)	Mdleve (Tsonga)	Mnisi farmers, Giyani farmers (*), South Africa	[64]
	Cattle: Milky latex applied on the cow third eyelid after protecting the eyes	Mdleve (Tsonga)	South Africa	[61*]
Inflammation of the mammary glands	Goats: Massage of the teats with heated leaves along decoction of leaves 1x/day during 5 days, VO	Nyamalimbwa, kabambabamba, kakobokobo, bihwiri (Mashi), umukoni (Kinyarwanda), katula (Kinande), potenge (Bembe), akasungusungu (Kihunde)	Kivu, Democratic Rep. of Congo (CA)	[65]
Snake bite	NEA: Leaf and root extract	Lal Manasa	Lodha etnia, Paschim Medinipur, West Bengal, IN	[66]
Theileriosis (East Cost Fever, bibagaliro, lokit)	NEA livestock	Not registered	Queen Elizabeth National Park, Uganda (EA)	[67]
	Cattle: Aerial parts, sap smeared at the swollen part	Nandele	Bulamogi country, Uganda (EA)	[68]
	Cattle Massage of glands with the latex	Not registered	Masai, Tanzania; Kenya (EA)	[69]

continued...

Table 1: Cont'd.

Symptom	Recipe	Vernacular name	Community/country	Refs.
	NEA: Warm cataplasm on the ganglions made from leaves mixed with two other specie's [h]; combined with three other species [i] water-pounded, ½ glass/day during 3 days VO	Kabambabamba (Mashi)	Bushi area, South-Kivu, Democratic Rep. of Congo (CA)	[70]
	NEA	Ntulasongo (Swahili / Sukuma)	Lake Victoria Basin, Tanzania (EA)	[71]
	Cattle: (a) Smear the latex of inside the lymph nodes after touching it with red-hot metal (Bokora tribe) (b) strap hided at the lymph node and smear latex (Pian tribe)	Lotome, longarwe (Ngakarimojong)	Karamoja, Northern Uganda (EA)	[72]
Ulcer	Not specified	Leiterinha, gota-milagrosa (Portuguese)	Juruena Region, Mato Grosso, Brazil	[45]
Wound	NEA: Stem sap directly on the wounds till total healing	Chandrya	Kokani tribals of Nasik district Maharashta, IN	[73]
Other Registers				
Girls' tattooing	Latex from stem barks and leaves	Bihwiri (Mashi dialect)	South-Kivu, Democratic Rep. of Congo (WA).	[47]
Gum for spearheads	Fresh sap used as glue for spearheads (Tepeth tribe)	Akwara	Tepeth tribe, Uganda (EA)	[72]
Living fence	Transplanted stems	Awas	Bokora tribe, Uganda (EA)	[72]
Ordeal	Latex; not specified	Not registered	Kisangani, Democratic Rep. of Congo (CA)	[53]
Repellent, insecticide	Hunting moles, not specified	Kambakamba (Shi), Umukoni, umurerabana (Kinyaruanda)	Bushi, South-Kivu, Democratic Rep. of Congo (CA).	[74]
Ritualistic, to cause fear to spirits (Umukoni)	Formulated with waterfalls water and "bad plants" sprinkled in the houses' corners, accompanied by incantation formulas and worship of familiar spirits	Gitinywa, Rutisukirwa	Rwanda	[75]

CA = Central Africa. EA = East Africa. WA = West Africa. IN = India. NEA = Non-specified animal (mammal). VO = via oral. (*) Eventually considered the same species, but originally registered as *S. cupulari* Boiss.[62] #Species were recorded as *Euphorbia umbellata*. [a] *Thunbergia alata* (l), *Hypoestes forskalaei* (l), *Melanthera scandens* (l), *Euphorbia schimperiana* (kamaramahano) (l), *Hygrophila spiciformis* (gangabukari) (l), *Sansevieria trifasciata* (l) (irago). [b] *Verbena officinalis* (l), *Euphorbia schimperiana* (l), *Crotalaria incana* (l). [c] *Vernonia thomsoniana* (l), *Phytolacca dodecandra* (l). [d] *Sida rhombifolia* (l), *Cynodon dactylon* (l), *Rhamnus prinoides* (l), *Zehneria scabra,* (l), *Pseudospondias microcarpa* (l) (umwifuzo). [e] *Berkheya spekeana* (l, ashes), *Chenopodium ugandae* (l, ashes), *Ficus ovata* (l, ashes). [f] *Fuerstia africana* (r), *Warburgia ugandensis* (b). [g] *Acokanthera schimperi* (r), *Warburgia ugandensis* (b). [h] *Coleus kilimanschari* (l), *Rumex bequaerti* (r), *Rubus apetalus* (r). [i] *Chenopodium procerum* (l), *Hibiscus calyphyllus* (l). b = bark, l = leaves, r = roots.

RESULTS

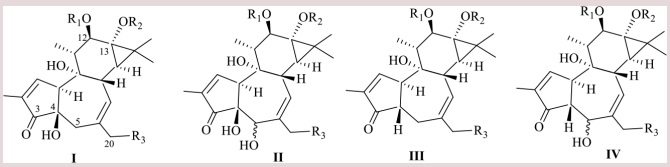
Traditional Use

The registers compiled in Table 1 concern the traditional use of species under the nomenclature of *Synadenium grantii*. Eight groups of disorders pooled by correlated targets encompassed thirty-four medicinal uses for the plant, as shown in Figure 1A. The main medicinal applications were antiparasitic (29.4%) and anti-inflammatory-related diseases (17.7%). By disregarding the undeclared cases, oral administration had the primacy (48.3%), followed by topical applications (37.9%) and other ways else (e.g., enema, dripping-into-ear, health ritual complement) (13.8%) (Figure 1B). A similar approach pointed to 57.5% of the recipes made with the leaves, followed by the latex (17.5%) and equal participation of the aerial parts or roots (10.6%) (Figure 1C). Few recipes involve mixing with fruit, milk or culinary oils, and importantly, five descriptions concerned composed recipes, eventually involving up to eight other plant species. From the

Table 2: **Triterpenes reported as constituents of *Euphorbia umbellata* (Pax) Bruyns.**

Steroid/Triterpene	Molecular Formula	Refs
ß-Sitosterol	$C_{29}H_{48}O$	[76,77]
Stigmasterol	$C_{29}H_{50}O$	[76,77]
Daucosterol	$C_{35}H_{60}O_6$	[77]
Lanosterol	$C_{30}H_{50}O$	[78,79]
Euphol	$C_{30}H_{50}O$	[76-82,86]
Citrostadienol	$C_{30}H_{50}O$	[80]
(3ß)-9,19-Ciclolanost-24-en-3-ol	$C_{30}H_{50}O$	[83]
Tirucallol	$C_{30}H_{52}O$	[76,78]
Euphorbol	$C_{31}H_{52}O$	[78]
Friedelanol	$C_{30}H_{52}O$	[79]
Germanicol	$C_{30}H_{50}O$	[77,86]
Germanicol acetate	$C_{32}H_{52}O_2$	[81]
Friedelin	$C_{30}H_{50}O$	[79]
Amirenone	$C_{30}H_{48}O$	[76]

Table 3: **Diterpenes isolated or characterized in *Euphorbia umbellata* (Pax) Bruyns.**



[1]Ia: R_1 = R_2 = acetyl, R_3 = acetoxy ($C_{26}H_{34}O_9$)[87]
[1]Ib: 12-deoxy-, R_2 = isobutyryl R_3 = H ($C_{24}H_{34}O_6$)[87]
Ic: R_1 = R_2 = acetyl, R_3 = phenylacetyl, C3 and C4: di-acetoxy (3,4,12,13-tetraacetylphorbol-20-phenylacetate = synagrantol A, $C_{36}H_{44}O_{11}$)[86,88,89]
Id: R_1 = R_2 = tigloyl, R_3 = H, C3 and C4: di-acetoxy (4-deoxyphorbol-12,13-ditiglate = synagrantol B, $C_{30}H_{41}O7$)[86]
IIa: R1 = tigloyl, R2 = isobutyryl, R3 = H ($C_{29}H_{40}O_8$)[85]
IIb: R1 = tigloyl, R2 = phenylacetyl, R3 = H ($C_{33}H_{40}O_8$)[85]
IIIa: R1 = tigloyl, R2 = isobutyryl, R3 = H ($C_{29}H_{40}O_7$)[84]
IIIb: R1 = tigloyl, R2 = phenylacetyl, R3 = OH ($C_{33}H_{40}O_7$)[85,90]
IIIc: R1 = phenylacetyl, R2 = undetermined polyunsaturated fatty acid, R3 = OH[85]
2IVa: R1 = tigloyl, R2 = isobutyryl, R3 = H ($C_{29}H_{40}O_7$)[85,90]
2IVb: R1 = tigloyl, R2 = phenylacetyl, R3 = H ($C_{33}H_{40}O_7$)[90]
[1]Ia and Ib have not been isolated, though they were reported as constituents in the *Euphorbia umbellata* latex, based on GC-MS analysis, during an anti-ulcer study. [2]5α-OH[85] or 5β-OH.[90]

Table 4: **Phenolic compounds reported for *Euphorbia umbellata* (Pax) Bruyns.**

Phenolic compound*	Refs.
Quercetin	[76,91]
Cyanidin 3-*O*-(2”-(5”’-(E-*p*-coumaroyl)-**β**-apiofuranosyl)-**β**-xylopyranoside)-5-O-**β**-glucopyranoside	
Cyanidin 3-*O*-(2”-(5”’-(E-caffeoyl)-**β**-apiofuranosyl)-**β**-xylopyranoside)	
Cyanidin 3-*O*-(2”-(5”’-(E-*p*-coumaroyl)-**β**-apiofuranosyl)-**β**-xylopyranoside)	
Cyanidin 3-*O*-(2”-(5”’-(E-feroyl)-**β**-apiofuranosyl)-**β**-xylopyranoside)	
Cyanidin 3-*O*-**β**-xylopyranoside-5-O-**β**-glucopyranoside	
Cyanidin 3-*O*-β-xyloside	
Kaempferol-3-*O*-**α**-L-rhamnpyranoside	[77]
Kaempferol-3-*O*-**β**-D-glucopyranoside	
3,3,4’-tri-*O*-Methylellagic acid 4’-*O*-**β**-D-glucopyranoside	

*All the compounds were isolated or characterized in the leaves.

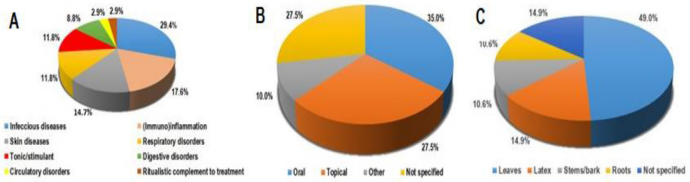


Figure 1: (A) Traditional human uses reported for *Euphorbia umbellata* (*Synadenium grantii*). (B) Reported medication administration route. (C) Parts of the plant constituting the reported recipes. See text for proportions based only on the specified information.

twenty-three preparations described for the leaves, one may infer that the exuding sap is relevant in eight of the cases, which would increase to 37.5% of the latex participation in the reported cases. By a similar approach, the veterinary applications in Table 1 converged toward ten animal diseases that could be pooled into four generic targets. In parallel with human applications, although showing a more striking trend, the antiparasitic and anti-inflammatory activities stood out with 80% of the veterinary applications (Figure 2A). Topical applications are by far the most reported cases (Figure 2B), a fact that may be due to the farmers' first appeal to fight theileriosis, which was a severe and lethal disease affecting the herds in the early colonial period of East Africa. Eighteen recipes could be compiled (Figure 2C), although six of them reported no details more than the part of the plant employed thereof. Among the identified recipes, eight (57.1%) were based on latex, and six other involved preparations using leaves, branches, bark and roots; the plant organ either alone or in binary combination (Figure 2C).

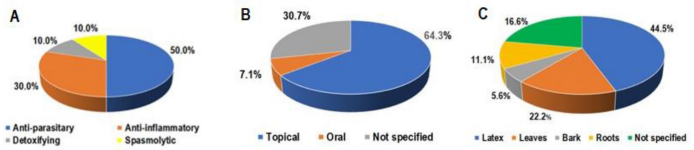


Figure 2: (A) Traditional veterinary uses reported for *Euphorbia umbellata* (*Synadenium grantii*). (B) Reported medication administration route. (C) Parts of the plant constituting the reported recipes. See text for proportions based only on the specified information.

Chemical Constituents

Triterpenes

The pharmacological investigation of *E. umbellata* has largely been based on its terpene composition, given that such a class of compounds is relatively abundant in the plant and is particularly concentrated in the sap. Tetracyclic triterpenes are always predominant, as corroborated by the marked common presence of euphol, lanosterol and tirucallol isomers in the latex and other extracts. The characterization of these triterpenes is usually accompanied by minor pentacyclic-related structures and sterols. Recently, phytol-type acyclic triterpenes have been detected in the latex of *E. umbellata*. Table 2 summarizes these findings and references.

Diterpenes

Since the first publications on the chemical content of latex, the diterpene profile of *E. umbellata* has been composed only of tiglian-type phorbol esters.[84-86] However, an ingol-type derivative has been recently reported in the leaves of this species.[77] These results are summarized in Table 3.

Polyphenols

There are few reports concerning the characterization of polyphenols in *E. umbellata*, among which it is possible to highlight the presence of rare anthocyanin containing the pentose sugar apiose on its furanosyl form,[91] hydrolyzable tannins and the flavonoids quercetin,[76] afzelin and astragalin,[77] as showed in Table 4.

Proteins

A low-weight single polypeptide chain glycoprotein (14 kDa), characterized as a carboxylesterase containing mostly neutral and acidic residues, was formerly purified from *E. umbellata* by chromatography on Sephadex followed by Sepharose-6B gel filtration.[92] Methods based on the finding of optimal pH and temperature for selective activity on diverse substrates, as well as specific inhibitors and kinetic development, pointed to the main presence of serine proteases in the latex. A protein with a molecular mass of 76 kDa with serine and histidine residues at the active site has been characterized.[93,94] In addition, a purified 34-kDa glycoprotein, also characterized as serine protease, has been associated with human fibrinolytic activity.[95] More recently, serinoproteases and cisteinoproteases were shown to predominate in the latex from specimens cultivated in two distinct locales in Brazil. Electrophoresis of samples pointed to additional bands corresponding to 149 and 94 kDa, with the occasional presence of aspartic protease and very low or absent metaloproteases.[96]

Biological properties

Table 5 systematizes twenty-four biological and pharmacological activities identified by separately driven literature compilation to the nomenclature *Euphorbia umbellata* and the two *Synadenium* synonyms. The major part of the reported experiments refers to *in vitro* or *ex vivo* tests (72%), with 28% of tests using rodents. The search for cytotoxic and antiproliferative effects on cancer cell lines is predominant among the *in vitro* assays, with antiparasitic and antibacterial ability being also explored targets. In most cases, there has been exhaustive testing of different plant extracts and

Table 5: Biological activities reported for *Euphorbia umbellata* and the synonymous *Synadenium* species.

Target	Part of the plant/preparation	Experimental details	Results	Refs
Euphorbia umbellata **(Pax) Bruyns**				
Antimicrobial	Stem bark. 7:3 EtOH:H_2O crude extract by exhaustive homogenizing (4 x 2d) the shredded dry material (CE). Chitosan-supported CE (1%-100% = MXMF).	MIC measurements: EE x *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* (agar diffusion, 1-100x)	Moderate inhibitory activity of the three strains by M100MF at pH 5.5 at 100%. CE: MIC 0.125 mg/mL (*S. aureus*); 1 mg/mL (*E. coli*). No activity against *E. coli* for loaded membranes. Correspondence with the release of phenolics.	[97]
	Stem bark. Ground dry material macerated in 7:3 EtOH:H_2O (8x 1 d); fresh extract chromatographed on flash column: Hx > $CHCl_3$ > AcOEt > MeOH (MF)	Evaluation of *Helicobacter pylori* inhibition by MF (1024-32 µg/mL). LC-QTOF-MS analysis of MF.	Inhibition by MF: 44.6% (at 256 mg/mL) of *Bacillus* growth and 78.6% of microbial urease at 1024 mg/mL.	[98]

Antioxidant	Stem bark. 7:3 EtOH:H_2O crude extract by homogenizing (4 x 2d) the shredded dry material (CE). Chitosan-supported CE (1%-100% = MXMF).	TPC: Folin-Ciocalteau, determination for chitosan-released compounds (gallic acid curve). Suppression of free radicals by DPPH$^{\bullet}$ and ABTS$^{\bullet+}$. Infrared, thermal data and X-ray diffractograms for the incorporated membranes; morphology by SEM.	TPC released maximum for M50MF (43% to 66% after 4hr). Higher antioxidant activity for M100MF, with IC_{50}: 280 ± 20 µg/mL (DPPH), 273 ± 6 µg/mL (ABTS$^{\bullet+}$).	[97]
	Stem bark. Ground dry material macerated in 7:3 EtOH:H_2O (8x 1 d); fresh extract chromatographed on flash column: Hx > $CHCl_3$ > AcOEt > MeOH (MF, LC-QTOF-MS analysis).	*In vitro* assays: DPPH, O_2, HOCl, TauCl, HRP, ABTS (*ex-vivo*, animal serum) (x quercetin). Correspondence with anti-ulcer mechanisms (for higher dosages). Role of nitric oxide synthase investigated.	MF: decrease in ulcerative lesion area (43.9%-89.9%), with large reduction for 200 mg/Kg. 5x < ranitidine; blocking of hemorrhage and edema. Promotion of COX levels involving increase in NO production. Probable role of MF in defenses involving NO production and reduction of glutathione levels. High antioxidant activity against several inducers.	[98]
Antirretroviral	Latex. Fresh material in 80% EtOH (1:10 v/v), filtration. Soluble fraction dried (EE)	*In vitro* reactivation of latent HIV and SIV in human primary CD4 lymphocytes after (i) cell viability, NF-κβ activation, (iii) surface markers and cytokine production. Tests in J-Lat cells model. Detn of pro-inflammatory cytokines. PKC isoforms activation.	Latency reactivation of HIV transcription with potency maintained below 0.01 µg/mL for EE. EE promotes nuclear translocation of NF-κB and modulates the expression of cell surface receptors, activation markers and cytokine secretion in primary CD4+ T cells. Th1 and Th17 immune response induced.	[99]
	Latex. 80% EtOH-soluble material: three phorbol-diterpenes isolated: P1, P2, P3	*In vitro* cell viability (MTT) and CD4 receptors downregulation in MT4 cells. HIV latency reactivation in J-Lat 10.6 cells. Serial dilutions. And ingenol B as positive control.	LAR effectiveness: 68–75% in the range of (µM) 9.7–0.097 (P1); 1, 8.85–0.088 (P2); 9.1–0.091 (P3), with 3 being effective down higher dilutions.	[90]
Antiulcerative	Stem bark. Ground dry material macerated in 7:3 EtOH:H_2O (8x 1 d); fresh extract chromatographed on flash column: Hx > $CHCl_3$ > AcOEt > MeOH (MF, LC-QTOF-MS analysis).	*In vivo* induction of gastric lesions (rats) by ethanol and indomethacin (50-200 mg/Kg, p.c. ranitidine 100 mg/Kg). T-SH analysis. Catalase assay. Histological analysis of the stomach. Correspondence with antioxidant results for higher dosages.	MF: decrease in ulcerative lesion area (43.9%-89.9%), with large reduction for 200 mg/Kg. 5x < ranitidine; blocking of hemorrhage and edema. Promotion of COX levels involving increase in NO production. Probable role of MF in defenses involving NO production and reduction of glutathione levels.	[98]

continued...

Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
Cytotoxicity Antiproliferative	Latex. Fr EtOAc (A), $CHCl_3$ (C) and sub-fr MeOH (M), CH_2Cl_2 (D), Et_2O (Et), EtOH (E)	*In vitro* growth inhibition of Hepa1c1c7, B16-F10, MDA-MB231 and FN-1, HUVEC, HASMC cells. Cytotoxicity by MTT (24hr, 2-30 µg/mL). MEP by confocal microscopy. Cell cycle phases by flow cytometry.	IC_{50} (µg/mL) fr A-E: 18.9-2.7 (FN-1), 7.8-4.3 (HASMC), 10-4.4 (HUVEC), 38.3-2.1 (BF16-F10), 11.7-1.9 (Hepa1c1c7), 16.7-2 (MDAMB-231). Et and M less toxic to normal cells. A, C, Et toxic to tumoral lines. Considerable MEP modulation with B16-F10 (no morphology change) and Hepa1c1c7cells treated with A or C. All fr increased tumor cells population with fragmented DNA.	[100]
	Latex. Hx extract (Soxhlet, 5hr) partitioned: Pet (PE), CH_2Cl_2 (DC), EtOH (ET) and MeOH (ME).	*In vitro* growth inhibition of HL-60, K-562 and Jurkat cells by MTT. SI calculation. HL-60: morphological and cell cycle (positive control) analyses; detn transmembrane potential; activation of caspases 3/7. Triterpene content detn by spectrometry. GC-MS and NMR.	HL-60 was the most sensitive cell lineage against DC and ET fractions. Indicatives of apoptosis induction, cell cycle alteration, cell depolarization and activation of caspases 3/7. SI > 22.44 for all cases. Active fr constituted of triterpenes and steroids.	[101]
	Latex. Sub-fractions (not detailed): ethyl acetate (A), $CHCl_3$ (C), MeOH (M), CH_2Cl_2 (D), ethyl ether (EE)	*In vitro* antiproliferative effect, antitumor and modulation of the mitochondrial electrical potential for MDA MB-231, 4T1. Cytotoxicity by MTT (2-30 µg/mL). Photomicrographs by LCM.	Decrease in cell viability and marked reduction in mitochondrial electrical potential for all cases. A and C were the most cytotoxic associated to higher selectivity referring to HUVEC cells (normal human endothelium).	[102]
	Latex. Not detailed sub-fractions: ethyl acetate (A), $CHCl_3$ (C),	*In vitro*: Effect of A and C on 4T1 cells. Cell viability by tb. Cell cycle, fragmented DNA and mitochondrial electrical potential quantified by flow cytometry and LCM. Cytotoxicity by MTT (2-30 µg/mL). Morphological analysis.	IC_{50} (24hr/48hr): 4.2/2.2 µg/mL (A); 5.9/3.0 µg/mL (C) (comparison with reported for other cases). Cytotoxicity of A and C due to apoptotic pathway modulation.	[103]
	Latex. Not detailed sub-fractions: ethyl acetate (A), $CHCl_3$ (C),	*In vitro*: Effect of A and C on B16-F10 (melanoma) and normal fibroblast FN1 cell lines. Cytotoxicity by MTT. MEP and cytoskeleton organization by confocal microscopy; cell cycle phases by flow cytometry.	Tumor inhibition (reduced density) by A (IC_{50} 13.7 µg/mL) and C (IC_{50} 2.3 µg/mL). Higher selectivity associated to reduced MEP and change in cell morphology. Apoptotic pathways modulation are suggested. FN1 cells changed morphology with cytoplasmic retraction: IC_{50} 13 µg/mL (A), 12.2 µg/mL (C).	[104]

continued...

Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
	Latex. Silica-adsorbed (Soxhlet, 5hr) extraction: Hx (H) > $CHCl_3$ (C), AcOEt (A) > MeOH (M1). H partitioned with CH_2Cl_2 (CH) > EtOH (E) > MeOH (M2).	*In vitro*: Fr effect on B16-F10 and 3T3 cells; MTT method; neutral red. SI calculation. *In vivo*: dorsal inoculated C57BL/6 mice with cultured B16F10 cells. Treatment after 10d (100 µL/animal, 15d).	Higher cytotoxicity after Hx partitioning (IC_{50} 2.82 to18.0 µg/mL, SI 3.4 to 1.1). No results from the *in vivo* assay. LC-MS/MS analysis points to phorbol constituents (mg/g extract) in: H (56.0), CH (1,245), E (462.0), M (143.0).	[105]
	Latex. Sequential Soxhlet extraction (5hr) with Hx (H) > $CHCl_3$ (C) > EtOAc (E) > MeOH (M). Sub-fr from H: Pet, CH_2Cl_2, EtOH. Euphol isolation.	*In vitro*: Fr, sub-fr, euphol effects on human HT-29, HCT166, MCF-7 and MDA-MB 231. Cytotoxicity by MTT. IC_{50} and SI calculations referring to HEK-293 cells. Caspase-3 and caspase-7 activation assessed for the most sensitive MDA-MB 231.	IC_{50} (µg/mL) fr and euphol (24hr/48hr): 77.9-25.7/48.7/19.4 (HT-29); 66.1-51.4/48.4-12.5 (HCT 116); 88.7-56.4/53.2-35.5 (MCF-4); 63.5-36.4/39.5-7.77 (MDA-MB 231); 162-113/106-76.5 (HEK-293). M ineffective to all cell lines. SI (all fr + euphol) (24hr/48hr): 1.44-6.03/1.57-5.77 (HT-29); 1.92-2.85/1.66-6.41 (HCT 116); 1.44-2.56/1.75-2.16 (MCF7); 2.05-3.91/2.68-9.85 (MDA-MB 231). Highest selectivity: MDA-MB 231 treated with A/48 hr. Apoptosis demonstrated.	[106]
	Latex. Fresh material fractionated in flash column: Hx > AcOE > MeOH. Bioguide isolation of euphol (E) and germanicol acetate (GA).	*In vitro*: HRT-18, HeLa, Jurkat cell lines: tb, MTT, neutral red, DNA quantitation, acridine orange and Hoechst staining; flow cytometry analysis. Controls: RPMI (-), vincristine, D- chlorambucil (+). Cell morphology evaluation. SI determination.	Toxicity dependent on conc for all cases; fr Hx being the most potent. CI_{50}: 30.50 ± 77.42 (HeLa), 26.16 ± 79.94 (HRT-18), 1.87 ± 2.22 (Jurkat). Low cytotoxicity of E and GA isolated from Hx fr.	[81, 107]
	Latex. 1% H_2SO_4-treated latex; insoluble eluted in sg column with AcOEt-Hx for euphol isolation (grad 1:9).	Inhibitory activity of euphol on leukemia cells: Jurkat, HL-60, K-562 (suspended), B16F10 and HRT-18 (adherent) x 3T3 normal cells. MTT method. SI calculation (48 h). Morphology of treated K-562 and B16F10.	Euphol (IC_{50} 72 hr, µM): 84.33 ± 11.76 (Jurkat); 49.36 ± 2.76 (HL-60); 34.56 ± 2.12 µM (K-562); 53.63 ± 10.16 (B16F10); 69.80 ± 7.31 (HRT-18). Low selectivity for 3T3 (SI 0.55) compared to lymphocytes and monocytes (SI > 2). Euphol unstable to gastric and intestinal fluids, plasma half-life of 2hr.	[82]

continued...

Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
	Stem bark. Ground dry material macerated in 7:3 EtOH:H_2O (8 x 1d, CBE): flash column with Hx > $CHCl_3$ > AcOEt > MeOH. GC-MS analysis.	*In vitro* antiproliferative effect on Jurkat cells (leukemia) of CBE and fractions. Evaluation by MTT, tb, DNA quantitation assay.	More active fr: $CHCl_3$ (steroids and triterpenes): IC_{50} (µg/mL) 29.00 ± 1.49 (24 h), 10.06 ± 1.48 (48 h), 4.83 ± 2.25 (72 h).	[108]
Molluscicide	Latex. Fresh material diluted in H_2O.	Lethality to *Biomphalaria glabrata* (BG, snail host of *S. mansoni*) exposed 24 hr to latex (WHO protocol). Toxicity to zebrafish (ZF, *Danio rerio*): 0.5-14 mg/L, 48hr).	LC_{10}: 0,50 (BG), 4,86 (ZF); LC_{50}: 1,36 (BG), 7,22 (ZF). LC_{90}: 3,69 (BG), 10,70 (ZF) mg/L. ZF less susceptible than BG.	[109]
***Synadenium grantii* Pax**				
Anti-inflammatory	Stem bark.Dry powdered material macerated in 70% EtOH 7x 24 hr (CBE): vacuum sg column: Hx (I) > $CHCl_3$ (II) > EtOAc (III) > MeOH (IV). Four triterpenes isolated by chromatography.	Carrageenan-induced paw edema in Winstar rats. Plethysmometry (60-240 min after injection); oral adm 50-300 mg/kg CBE (x ibuprofen): biochemical parameters, organ weighing; check for stomach injury.	ECB reduces edema at 50 mg/kg at any time of evaluation, emulating the effect of ibuprofen. Erratic positive results for higher doses. No tests with isolated compounds	[79]
	Latex. Partition (Soxhlet, 5 h): hexane (H), chloroform (C), ethyl acetate (A) and methanol (M). Tri- and diterpenes profiles characterized by GC-Q-ToF and NMR.	Activation of classical (CA), alternative (AP) and lectin (LP) complement pathways. Hemolytic and lectin pathway activation assays. Chemotaxis assay (human neutrophils, *in vitro* leukocyte migration). Heparine (Hep) as positive control.	CP (416.5 µg/ml): inhibition activated (%) 28 (M), 20 (E), 33 (Hep); 27 (C) 0 (H). AP: inhibition activated (%) by 19 (M), 25 (E), 20 (C), 44 (H), 44-100 (Hep); dose-response effect, IC_{50} (µg/ml): 5.29 (H), 13.24 (Hep). LP: (416.5 µg/ml) inhibition (%) of 16 (E) and 19 (H); 69-51% (C, 125.0-62.5 µg/ml), 79-39% (H, 125.0-31.2 µg). Immunomodulation suggested for all extracts.	[110]
Antioxidant	Stem bark. Dry powdered material macerated in 70% EtOH 7x 24 hr (CBE): vacuum sg column: Hx (I) > $CHCl_3$ (II) > EtOAc (III) > MeOH (IV). Four triterpenes isolated.	TPC assessment. *In vitro* methods: $ABTS^{\bullet+}$; $DPPH^{\bullet}$; HOCl; $O_2^{\bullet-}$ (x resveratrol = R); inhibition of human myeloperoxity (MPO); hemolysis.	TPC 404.8 mg/g extract. Strong antioxidant activity: (3.57 x 0.50R) $ABTS^{\bullet+}$; (12.1 x 63.4R) $DPPH^{\bullet}$; (1.14 x 1.02R) HOCl; (158,1 x 143.1R) $O_2^{\bullet-}$; (8.45 x 0,40R) MPO; (5.17 x 2.37R) hemolysis.	[79]

continued...

Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
	Aerial parts. Ground dry material extracted sequentially (6hr) in soxhlet with Hx (H) > AcOEt (AE) > 70% EtOH (AL).> MeOH (ME).	TPC assessment (Folin-Ciocauteau). *In vitro* inhibition of DPPH radical, superoxide and hydroxyl radical, correlation with polyphenols quantity. Sample tested samples (x ascorbic acid, AA) at 20-1280 µg/mL.	TPC (mg/g gallic acid): range 40.21 ± 0.10 (ME) to 9.10 ± 0.22. IC_{50} (µg): DPPH: 424 (AL), 284 (ME), 211 (AE), 531 (H), 16 (AA); superoxide (µg): 401 (AL), 226 (ME), 298 (AO), 742 (H), 59.3 (AA); $HO^{\bullet}$ (conc-dependente, µg): 420 (AL), 268 (ME), 195 (AE), 390 (H), 66 (AA).	[111]
Antiparasitary	Leaves. Dry powdered material macerated in $CHCl_3$ (5x) (EC) > fractn $CHCl_3$:MeOH > charcoal depigmentation > sg column, grad AcOEt:Hx > prep TLC. Isolated euphol, germanicol, phorbols A, B.	MRC-5 (lung fibroblasts) incubated with extract; Alamar blue method. Parasite's lactate dehydrogenase assay. *In vitro* tests (x control): *P. falciparum* (lactate dehydrogenase); *T. brucei* (trypomastigote), blood cells, hemoflagellates; *T. cruzi* (amastigotes): parasitemia reduction.	Extract: IC_{50} (µg/mL): 8.11 (*T. brucei*), 23.70 (*P. falciparum*), 2.21 (*T. cruzi*). Isolated cpds not tested.	[86]
Antiretroviral	Latex in 80% EtOH (1:10 v/v), filtration > drying > soluble fraction (EE).	EE-treated peripheral blood mononuclear cells (1-0.01 µg/mL, 24 h). Evaluation *in vitro* of cytokine production, viral replication and viability of CD4+ T cells.	EE (0.1 µg/mL): several inflammatory cytokines produced, but not IL-10. Increasing levels of CD4+ and CD8+ T cells producing IFN-γ and IL-17 and other subtypes producing IL-21+. Response to EE: levels of IL-1β, IL-6 and TNF-α correlated positively with rate of viral replication in culture.	[112]
Cytotoxicity Antiproliferative	Latex. (i) Popular recipe (PR): 18 drops in 1 L of water; (ii) Fresh sample fractn flash column: Hx > $CHCl_3$ > AcOET > MeOH. Hx fractionated in MeOH (FM) and Hx (FH). FH refract sg column: euphol (E) and citrostadienol (C).	Antiproliferative activity at different conc latex (L) and PR on B16F10 cells (melanoma) by MTT, tb and cell cycle (flow cytometry). *In vivo*: cancer cells sq in C57BL6 mice, treatment after 10 d (3x d). Histological analysis of the organs (hematoxylin-eosin staining)	*In vitro* inhibition 48 hr: 98% (PR) and 100% (L) (tb, 48hr); 40% (PR) and 64% (L) (MTT). (L): dose-dependent cell death. E non-toxic, C weakly toxic. *In vivo*: 40% tumor reduction. Necrosis and large number of tumor cells with nuclear hyperchromaticism, pleomorphism and eosinophilic cytoplasm in affected areas. Atypical mitosis and metastasis to lung tissues.	[80]
	Leaves. Dry powdered material macerated in $CHCl_3$ (5x) (EC) > fractn $CHCl_3$:MeOH > charcoal depigmentation > sg column, grad AcOEt:Hx > prep TLC. Isolated: euphol, germanicol, phorbols A, B.	MRC-5 (lung fibroblasts) incubated with different extract conc, Alamar blue method.	IC_{50} 26.49 µg/mL, *marginal* cytotoxicity to MRC-5.	[86]

continued...

Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
	Stem. Fresh material macerated (MeOH, 7 d), dried and suspended in 1:1 MeOH-H_2O > $CHCl_3$ partition (CE) and AcOEt. CE: sg column, grad AcOEt/Hx. Isolated 3,4,12,13-tetra acetylforbol-20-phenylacetate (F).	Fractions tested on tumor lines: U-251 (glioma), MCF-7 (breast), NCI/ADR-RES (multi-resistant ovary), 786-0 (kidney), NCI-H460 (lung), HT-29 (colon), K562 (leukemia). *In vitro* Total Growth Inhibition (TGI) evaluated by sulforhodamine B and MTT (doxirubicin as control).	TGI between 5.3-11.7 µg/mL for most lineages, slightly more active to kidney, glioma and breast, depending on the fraction. F: TGI 24.1- 31.1 µg/mL for 3 cases. Though not very active, F might contribute with some of the more promising results.	[88]
	Latex in water (1:10 w/v) > sequential dilutions to generate 0.75-6 mg/ml. Crude material characterized by pH and phytochemical screening. Presence of phorbol ester (dPPA) suggested by mass fragmentation.	Inhibitory effect (MTT) on two canine prostatic carcinoma cell lines ('non-metastatic blend' PC1 and 'metastatic blend' PC2) at 24, 48, 72 hr. Previous phenotypes and morphological evaluation of both lineages cultured in PrEBM.	PC1 formed colonies and tubular-like structures; PC2 grew isolated. IC_{50} (mg/ml) 0.847 (PC1, dose-dependent) and 0.607 (PC2). Best effects with 6 mg/ml for both cases; evenly answers from both lines at 72 hr.	[113]
Cardiovascular action	Latex. Diluted in EtOH (1:2), stirring, decantation. Residue extracted with 2x EtOH, dried, diluted in EtOH up to 100 mg/mL (stock, EE)	Stock solution as fine suspension in saline: i.p. in mice. Hypothermic effect after pyrogen-induced fever i.v. in anesthetized dogs. Monitoring of carotid pressure and urinary flow; ECG recorded. Effect on isolated heart of frogs and various animal tissues from different origins.	No direct action on tissues isolated from several animals (0.02-2.56 µg). Low dose EE (0.1-0.4 mg/kg) induces slight increase in blood pressure and diuresis, but no change in adrenaline, acetylcholine, 5HT, histamine, carotid occlusion or vagal stimulation. High doses (0.6-1.0 mg/kg) induce bradycardia and antidiuresis, with fatal pressure drops and pulmonary edema.	[114]
Coagulation	Latex. Monomeric glycoprotein (LGP, 34,4 KDa) purified by precipitation and gel permeation chromatography	Evaluation of clotting (fresh human plasma in citrate medium); recalcification time (RT), prothrombin time and others. Hydrolysis studies with protein fragments characterization.	LGP induced clot formation with citrated human plasma and reduced RT from 165 to 30 s. LGP did not prolong anticoagulant effect even at higher conc. Purified fibrinogen did not clot even at high protein conc and longer incubation. Although inducing procoagulantion, LGP hydrolyses partially cross-linked fibrin clot.	[95]

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Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
Effect on dysmenorrhea	Stem and leaves. MeOH extract (ME) and isolated 3,4,12,13-tetra acetylforbol-20-phenylacetate (F)	Estradiol-induced (i.p.) dysmenorrhea in Swiss female mice orally treated with ME, F or control drugs, followed by i.p. oxytocin. Evaluation of abdominal writhing. Uterus weighted and analyzed by morphometry.	Inhibition of abdominal writhings with ID_{50} 25.8 (8.38-77.7% for 1-100 mg/kg MS) and 15.10 (49.4-65.2% for 0.1-40 mg/kg F). F and ME induced uterus reduction associated with edema and leukocyte migration. F partially active in dysmenorrhea.	[89]
Fibrinolytic action	Latex. Monomeric glycoprotein (LGP) purified by precipitation and gel permeation chromatography	Evaluation of caseinolytic (latex and GLP incubated with different conc casein) LGP (incubated GLP with different conc fibrinogen) and clotting activities. Experiments with protease inhibitors.	LGP is a serine protease that might act on multiple sites of fibrinogen. Glycoprotein with human fibrino(geno)lytic activity that differs of plasmin regarding possible therapy for stopping bleeding and heal wounds.	[95]
Gastric protection	Latex pure (EB1) or diluted (18 drops in 1L H_2O) (EB3). Dry material macerated in 7:3 EtOH: H_2O (7 d) > lyophilization (EB2).	Gastric lesion induced by sq indomethacin and oral ethanol (x ranitidine / omeprazole), Winstar rats.	Protection of injury: 90% (EB1) and 6% (EB3).	[87]
Hemagglutination	Latex. Acetone-precipitated lectins (L) diluted in water (1:20) and centrifuged. Elution in sepharose-6B: saline > 0.1M galactose	Inhibition of lectin-induced blood agglutination by various sugars, on diverse animals' and human (types A, B, O) erythrocytes	Human blood: L agglutinates O-group more tightly than A- and B- at 2 µg/mL. Red blood cells from guinea pig, rabbit and rat need higher concentrations of lectin; while those from dogs, sheep and cows do not agglutinate. Galactose, lactose, raffinose and melibiosis reversed the lectin action.	[115, 116]
	Root. Separation of lectins (no method cited)	Erythrocytes from patients with 11 types of cancer in contact with several conc of lectin, 30 min. Hemoagglutination observed with the naked eye and microscope	Significant activity only in the case of breast cancer. Probable involvement of sugar receptors on the cell surface.	[117]
Hemostatic	Latex. Homogenization (0-5°C), filtration, centrifugation. Supernatant = crude enzyme extract (CEE)	Proteolytic activities, protease, gelatinase, milk clotting and whole blood clotting assay. *In vivo*: mice, bleeding test and induced wound clotting time.	3.53 ± 0.12 mg/g protein in the latex. Protease activity 9.77 ± 0.40 U/g. Milk clotting activity 39.9 ± 0.33. Gelatin test 4.04 ± 0.36 U/g. Latex reduces the bleeding time 4x in mice.	[118]

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Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
Hypothermic action	Latex. Diluted in EtOH (1:2), stirring, decantation. Residue extracted with 2x EtOH, dried, diluted in EtOH up to 100 mg/mL (stock, EE)	Stock solution as fine suspension in saline: i.p. in mice. Hypothermic effect after pyrogen-induced fever in albino rats and rabbits with negative control (M/F, British Pharmacopoeia) by measuring rectal temperature (30-150min).	LD_{50} 51.3 mg/Kg (i.p., mice). Notable reversible and dose-dependent hypothermic activity of EE for all doses tested (1-20 mg/Kg) in both animal types.	[119]
Molluscicide	Leaves. Ethanol extract (maceration) (EE)	EE: Letality for *Biomphalaria glabrata* (OMS guideline), 100-5.0 µg/mL, positive control niclosamide.	LC_{50} = 40.0 µg/mL (regarded as good)	[120]
Mutagenicity Genotoxicity	Latex. Dilution (x6) in water: 0.8% (stock solution) to 0.025%.	Micronucleus frequencies and chromosomal aberrations in *Allium cepa* roots exposed to different latex conc. Mitotic index calculation. H_2O and $CuSO_4$ as negative and positive controls.	All tested conc were cytotoxic to the root cell cycle. Mutagenic/genotoxic effect in meristematic cells of *A. cepa*, with high micronucleus averages compared to the control; lowest frequency for 0.4% latex.	[121]
Nematicide	Latex. Separation of solids x serum by centrifugation (assessment of proteolytic activity).	Protease activity (citrate/casein) and chitinase (citrate/chitin). Electrophoresis 80 V. Lethality degree against *Meloidogyne incognita* (MI) and *Panagrellus redivivus* (PR)	Proteolytic activity in latex serum (530 ± 46 U/mL). Null activity for chitinase. Lethality to MI (100%) and PR (72%) attributed to proteases	[122]
Skin toxicity	Latex. Homogenization (0-5°C), filtration, centrifugation. Supernatant = crude enzyme extract (CEE)	OECD guidelines, 1-14 days.	No skin-irritant effect.	[118]
Skin-irritant	Latex. Bioguided isolation of 12-O-tigloyl-4-deoxyphorbol-13-isobutyrate	Mouse ear-irritant activity	Non-specific evaluation, qualitative evaluation	[84]
Toxicity	Latex pure (EB1) or diluted (18 drops in 1L H_2O) (EB3). Dry material macerated in 7:3 EtOH: H_2O (7 d) > lyophilization (EB2).	Toxicity: *In vivo* (oral in rats) assessment of biochemical parameters. Lethality to *Artemia salina* (samples 1000-1 µg/mL).	Lethality for *A. salina* = LC_{50} 26.58 µg/mL (EB1, high toxicity) and 778.66 µg (EB2, low toxicity). Higher enzymatic activity in hepatic parameters for EB1. No evident macroscopic changes.	[87]
	Latex solutions	Static system with seeds of *Lactuva sativa* (lettuce), *Raphanus sativus* (radish): conc latex x root growth and *Artemia salina*	Lower extract concentrations associated with increased germination (data not shown)	[123]
***Synadenium umbellatum* Hook f.**				
Angiogenic	Latex. Aqueous solution 1: 9 *v/v* > dilutions to reach 10 and 20 mg/mL	Rate of increase in the vascular network of the chorioallantoic membrane in embryonated chicken eggs. H_2O as negative control. Histological method with images	Significant angiogenic activity due to increased embryo vascularity: 49.1% and 52.9% for 10 and 20 mg/mL of pure latex x 32.6% H_2O.	[124]

continued...

Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
Antibacterial	Latex. Fresh material dissolved in saline solution	Cytotoxicity to peritoneal macrophages by MTT. Evaluation of the latex ability to (i) inhibit agar diffusion of cultures of *S. aureus*, *E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae*; and (ii) elicit phagocytosis of *S. cerevisiae* by macrophages. Phagocytic Index (PI) assessed *in vitro*	Dose-dependent cytotoxicity. Non-toxic concentrations ineffective against the tested organisms. PI increased with latex titers 1:30, 1:60 and 1: 120, implying a gradual improvement in the inflammatory response against infectious agents.	[125]
Cytotoxicity Antiproliferative	Aerial parts. Air-dried ground material exhaustively macerated in 95% EtOH (EE)	Cell lines K-562 and Jurkat (leukemia). Viability by tb (0.007-1 mg/mL, 24 h). Morphological changes by microscopy. Cell cycle (+ extract, 24 h), RNAse, flow cytometry. Intracellular ROS (+ EE, 12/24 h). Potential of the mitochondrial membrane, phosphatidylserine, caspase activity (colorimetry for protease)	K-562 selected (IC_{50} 0.041 viability). EE interferes in the opposite way in different phases of the cycle and increases dose-dependently the intracellular ROS (111% in 24 hr, with ≤118% hyperpolarization of the mitochondrial membrane). Increasin caspase 9 activity, suggesting its participation in apoptosis.	[126]
Anti-inflammatory	Leaves. Dried ground material macerated (3 x 5hr) (EE) > MeOH (4°C, 18hr) + 7:3 H_2O > seq partition Hx (HF), $CHCl_3$, (CF), MeOH (MF)	Croton oil-induced ear edema and carrageenan-induced peritonitis (x dexamethasone). Doses 25-100 mg/Kg.	Reduction of ear edema: 30-60% (EES) and 20-62% (MF < positive control) and intraperitoneal leukocyte migration.	[127]
Antimutagenic	Latex Dilution in water (not detailed)	AMES test on *Salmonella typhimurium* strains (2 strains, positive 4-nitroquinoline and sodium azide). Dose range: 50-500 µg	No mutagenic effect on the tested strains for doses up to 100 µg. Higher doses synergize DNA damage inductors.	[128]
Antinociceptive	Leaves. Dried ground material macerated (3 x 5hr) (EE) > MeOH (4°C, 18hr) + 7:3 H_2O > seq partition Hx (HF), $CHCl_3$, (CF), MeOH (MF)	Albino mice: HOAc-induced writhing test (x indomethacin), formalin-induced paw licking, tail withdrawal. EE at 25-100 mg/kg range.	EES and MF: (i) dose-dependent antinociceptive activity in the writhing test (24-55% reduction; positive control); (ii) EES reduces both formalin phases (49% and 73%); opioid mechanism involved.	[127]
Antiparasitary	Latex. Lyophilized raw material embedded into sg: seq extraction with Hx, $CHCl_3$, AcOEt, EtOH	*In vitro* activity against *Leishmania amazonensis*: doses 7.81-250 µg/mL (promastigotes); 62.5-250 µg/mL (amastigotes in macrophages). NO production by infected macrophages.	Leishmanicidal activity by the highest doses of AcOEt fr (IC_{50} 37.43 on promastigotes), independent of NO production.	[129]

Table 5: Cont'd.

Target	Part of the plant/preparation	Experimental details	Results	Refs
Antitumoral, Antiangiogenic	Aerial parts. Exhaustive maceration in 95% EtOH of the material dried in the air and ground (CEE). Fr: $CHCl_3$ (CF), Hex (HF) and MeOH-H_2O (ME)	Cell viability, cytotoxicity in K-562 cells and Ehrlich's ascitic tumor (EAT) at (mg/mL): 0.018-2.32 (CF), 0.006-0.76 (HF), 0.018-2.34 (ME), 24/48 hr (MTT and tb). *In vivo*: EAT implanted in Swiss mice (after treating 10 d). Treatment (after 24hr): CEE (5-25 mg/Kg/d), CF, HF at equivalent doses. Survival period evaluated x control.	*In vitro*: Cl50 0.4 mg/ml (EEC); 0.1 mg/ml (HF) and 0.8 mg/ml (CF). *In vivo*: best result from CEE (25 mg/kg/d) increased survival and reduced the amount of tumor cells, being antiangiogenic by reducing the vascular endothelial growth factor.	[130]
Larvicide	Latex. Fresh material diluted in water to 200 ppm (stock solution, SS)	*Aedes aegypti* 3rd stage larvae growth 48 hr in biological chamber. SS dilution ranging from 150 to 40 ppm; positive control.	Increased larvicidal activity with higher doses. LC_{50} 65.24 ppm. Total mortality at the highest dose after 48 hr.	[131]
Mutagenicity Cytotoxicity	Leaves. Dry ground material macerated in 95% of EtOH (3x 1:5 m/v) (EE)	Cell viability (MTT and tb): 2×10^6 mouse marrow cells incubated with EE (40-0.312 mg/mL, 12-48hr). *In vivo*: 10-25-50 mg/kg EE orally; bone marrow analysis, positive (cyclophosphamide) and negative control. Formation of micronuclei evaluation.	EE cytotoxic at all measured intervals: IC_{50} 7.9-3.6 (trypan blue); 3.6-18 mg/mL (MTT) for 12-48 hr. EE dose-dependently increased the number of micronuclei by 110% (20 mg/kg) and 121% (50 mg/kg). Lower doses were not statistically significant.	[132]
Toxicity	Latex. Fresh material (L): EtOH extract of leaves and branches (EE) (no details)	*In vivo*: guidelines OECD. ALD in mice (i.p.) linearly decreasing doses (½ stepwise). LD_{50}: EE (i.p. single dose) of 74-250 mg/Kg (males, M), 98-375 (females, F) for L. and 98-500 mg/Kg (M) and 74-375 mg/Kg (F).	ALD (mg/Kg): 167 (M) and 110 (F). LD_{50} (L): 168.95 mg/kg (M), 110.36 mg/kg (F). LD_{50} (EE): 156.88 mg/kg (M); 163.68 mg/kg (F, 95 mg/kg). Latex more toxic to females as a trend.	[133]
	Leaves. Dry ground material macerated in EtOH 95% (EEF)	Acute (2000 mg/Kg) and subacute toxicity (50-200 mg/Kg) in rats (OECD 2001/423 and 1995/407). Histopathological analysis. Body weight measurements, organ weights and variation in daily physiological habits	Non-toxic nor lethal EEF or LX at 2000 mg/kg. No macroscopic changes, nor variations in the organ's relative weights. Congestion and leukocyte infiltration in the liver, kidneys and lung for LX, without changes for EEF. No significant hematological changes. No variations in habits.	[134]

AcOEt: ethyl acetate. adm: administration. $CHCl_3$: chloroform. conc: concentration. cpd: compound. d: day. Detn: determination. Et_2O: ethyl ether. EtOH: ethanol. evpn: evaporation. fr: fraction. fractn: fractionation. grad: gradient. Hx: *n*-hexano. MeOH: methanol. PEt: petroleum ether. sg: silica gel. Notation ">" in the first column means "followed by".

fractions derived from them, which eventually drives the positive results to triterpenic constituents, especially the tetracyclic isomers euphol and lanosterol plus tirucallol. The anticancer capacity of euphol has been tested in rodents. Skin-irritant properties, anti-inflammatory and anti-ulcerative activities, among a few others, complete the panel of isolated terpenes tested in animal models. Three phorbol esters isolated from the latex, 20-deoxyphorbol-5β-hydroxy-12-tiglate-13-isobutyrate, 20-deoxyphorbol-5β-hydroxy-12-tiglate-13-phenylacetate and 4-deoxy-4β-phorbol-12-tiglate-13-phenylacetate, were shown to be highly effective *in vitro* to reverse the latency of HIV in infected cells. Toxicity-related tests have also been reported for latex and extracts from other parts of the plant. Bioassays employing *Artemia salina*, *Biomphalaria glabrata*, *Aedes aegypti* larvae, embryonated chicken eggs, lettuce seeds and others have also been reported. Some entries in Table 5 refer to bioassays based on the latex proteolytic enzymes, notably on assaying their activity on human fibrinogen and fibrin clots, as well as other tests involving erythrocyte agglutination and anticoagulant activity. In addition, the latex proteases were suggested to be responsible for the significant nematicidal property observed against *Meloidogyne incognita*.

CONCLUSION

This review shed light to the trajectory of the various botanical synonyms used for the species *Euphorbia umbellata*, since its first found by an occidental explorer, which coincides with the history of the search for the outsource of the Nile River. Three reasons justify the survey of historical records about the saga of the introduction of the plant in England since its collection in Africa. The first concerns the recognition of the origin of access to its genetic heritage and associated traditional knowledge, which today has a strong impact on the elaboration and commercialization of products from natural sources. Second, the tracking of the process of botanical determination of the species in focus reveals the strong contribution of botanists to research advances in other disciplinary areas. Finally, the multitarget medicinal properties of *E. umbellata* became evident from the gathered data related to its traditional uses in Africa. Several biological targets currently investigated regarding the effect of the latex and leaves of *E. umbellata* have some parallel with the early homemade remedies, especially those acting on inflammation-related disorders. In Brazil and some neighboring countries, plant usage underwent a translational movement to extensively reach, more recently, the treatment of several types of cancer, arthritis pains and, eventually, HIV-infected people. Such a popularization seems to reflect a way to find a succedaneum for the *E. tirucalli* latex, whose medicinal use has later been strongly inhibited in Brazil, as the regulatory normative in force precluded any development of phytomedicines based on this species due to its content in phorbol esters. Nonetheless, it may be pointed out that, different from *E. tirucalli* and many other congener species, the *E. umbellata* latex and leaves are devoid of phorbol bearing fatty acids as esterifying groups, a feature that is highly associated with the toxicity and tumor-promoting properties of these series of compounds. In practice, such a lower toxicity of *E. umbellata* would putatively be reinforced by the quite low daily doses and a favorable posology associated with the current popular recipes. In this sense, any information retrieved from ancient records around the world is valuable to comprehend the ethnomedical breadth of this species usage. Currently, the most significant progress with latex and leaves of *E. umbellata* lies in the investigation of their anticancer and anti-HIV properties of their terpenoid constituents. The tetracyclic triterpene eufol and phorbol esters with aromatic residues have led the investigation of the anticancer and antiviral properties of *E. umbellata* latex, respectively.

Authors' contribution

Antonio C. Siani: Conceptualization, data analysis, writing, review and editing. Lívia A. Santos: Conceptualization, literature search, data collection, organization and analysis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

3T3: Murine embryonic fibroblast cell line; **4T1:** Murine triple-negative breast cancer cell line; **786-0:** Human renal carcinoma cell line; **ABTS•+:** 2,2'-azino-bis(3-ethyleneb enzothiazoline-6-sulfonic acid)$^{\bullet+}$; **ALD:** Acute lethal dose; **B16F10:** Murine melanoma cell line; **COX:** Cycloxigenase; **DPPH$^{\bullet}$:** 1,1-diphenyl-2-picrylhydrazyl radical; **EAT:** Ehrlich's ascitic tumor; **FN-1:** Normal human fibroblast; **GC-MS:** Gas Chromatography coupled to Mass Spectrometry; **HASMC:** Human Aortic Smooth Muscle Cells; **HCT166:** Human colon cancer cell line; **HeLa:** Human papillomavirus-related endocervical adenocarcinoma cell line; **Hepa1c1c7:** Murine Hepatocellular carcinoma cell line; **HIV:** Human immunodeficiency virus; **HL-60:** Human adult acute myeloid leukemia cell line; **HOCl:** Hypochlorous acid; **HRP:** Horseradish peroxidase; **HRT-18:** Human colon adenocarcinoma cell line; **HT-29:** Human colorectal adenocarcinoma cell line; **HUVEC:** Human Umbilical Vein Endothelial Cells; **i.p.:** Intraperitoneal injection; **i.v.:** Intravenous administrations; **J-Lat 10.6:** Subclone derived from pseudotyped HIV-1-infected Jurkat cells; **Jurkat**

cells: Human leukemia (T lymphocyte) cell line; **K-562:** Human chronic myeloid leukemia cell line; **LAR:** Latency-reversing agent; **LC:** Lethal concentration; **LCM:** Laser confocal microscopy; **LC-QTOF-MS:** Liquid Chromatography coupled to Quadrupole Time-of-Flight Mass Spectrometry; **MCF-7:** Human breast carcinoma cell line.

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