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Review

Why do Euphorbiaceae tick as medicinal plants? A review of Euphorbiaceae family and its medicinal features

Julius T. Mwine[1]* and Patrick Van Damme[2]

[1]Faculty of Agriculture, Uganda Martyrs University, Nkozi, P. O. Box 5498, Kampala, Uganda.
[2]Faculty of Bioscience Engineering, Tropical and Subtropical Laboratory of Agronomy and Ethnobotany, University of Ghent, Coupure links 653, 9000 Ghent, Belgium.

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Euphorbiaceae is among the large flowering plant families consisting of a wide variety of vegetative forms some of which are plants of great importance. Its classification and chemistry have of late been subjects of interest possibly because of the wide variety of chemical composition of its members, many of which are poisonous but useful. In this review, we have tried to demonstrate why Euphorbiaceae are important medicinal plants. Two important issues have come up. The worldwide distribution of the family exposes its members, to all sorts of habitats to which they must adapt, therefore inducing a large variety of chemicals (secondary substances) that are employed for survival/defense. Succulence and the CAM (crassulacean acid metabolism) pathway that characterize a good number of its members were quoted as some of the adaptations that aid colonization and survival to achieve this induction. We have also found out that medicinal properties of some of its species may be due to stress factors that characterize most habitats of the family. Varying stress factors like temperature, salinity, drought and others were seen to operate in tandem with genetic factors such as gene expression and mutation loads to bring about synthesis of a wide assemblage of secondary substances that may probably be responsible for the family's medicinal nature. It was concluded that the family is a good starting point for the search for plant-based medicines.

Key words: Bio-synthesis, ethnomedicine, secondary metabolites, stress physiology.

INTRODUCTION

Family Euphorbiaceae as traditionally delimited (Euphorbiaceae *s.l.*, Webster 1994) is one of the largest families of flowering plants, composed of over 300 genera and 8,000 species. According to the latter author, the family is very diverse in range, composed of all sorts of plants ranging from large woody trees through climbing lianas to simple weeds that grow prostrate to the ground. Members are widely distributed all around the world constituting both old world and new world plants some of which are yet to be identified. Many family members are inhabitants of tropical climates surviving hot dry desert conditions while others are rainforest trees and herbs. The family consists of species of great economic importance like *Ricinus communis* L. (castor oil plant), *Manihot esculenta* Crantz (cassava) and *Hevea brasiliensis* Willd. Ex. A. Juss (rubber tree) among others but also noxious weeds like *Euphorbia esula* L. and *Euphorbia maculata* L. (Schultes, 1987). The implication of this is that Euphorbiaceae is a complex family with a lot of research potential.

Complexity in habitat range and variability in morphology and genetics has made Euphorbiaceae classification difficult. Homogenous families have their classification based on simple, unique characteristics that cut across the family, e.g. monocotyledony and parallel venation for family Poaceae. In the case of Euphorbiaceae, there appears to be no particular and easily observable feature that can be used for its

*Corresponding author. mwinej@yahoo.com

classification. In agreement with this, Webster (1994) states that no single feature characterizes the Euphorbiaceae. Instead, he enumerates several anatomic features like wood structure, laticifer type, trichomes and nature of stomata as being important for family classification, while others like pollen nuclear numbers, exine structures, type of pollination and inflorescence types are important for classifying genera, tribes and subfamilies.

According to Webster (1975), there have been several Euphorbiaceae classifications dating as far back as 1824 by taxonomists like Adrien Jussieu who identified the family's genera and Jean Mueller who provided a first detailed classification of the family into subfamilies, tribes and sub-tribes. Webster (1975) believes that Mueller's classification of 1866 was a milestone in Euphorbiaceae classification. He argues that Mueller was the first to use coherent phylogenetic characteristics that for a long period withstood the test of time.

Using Mueller's classification as a skeleton, Webster employed phylogenetic structures such as pollen morphology and anatomy to come up with his own classification. He divided the family into five subfamilies that is, Acalyphoideae, Crotonoideae, Euphorbioideae, Phyllanthoideae and Oldfieldoiideae (Webster, 1975). According to this classification, the first three subfamilies are characterized by one ovule per locule (uni-ovulate) while the last two have two ovules (bi-ovulate). For several decades, this was the (traditional and) generally accepted form of classification.

As is common with such large and diverse families like Euphorbiaceae, there was constant pressure and proposals to re-define the family boundaries, to exclude genera that appear il-fitting and include those that appear left out, but also to carry out internal re-organization of subfamilies, tribes and sub-tribes. Phytochemical and molecular phylogenetic studies eventually accumulated evidence pointing to non-monophyly of Euphorbiaceae (Seigler, 1994b; Tokuoka and Tobe, 1995). This culminated into partitioning of the traditional Euphorbiaceae into five families, where only uni-ovulate subfamilies constituted family Euphorbiaceae *sensu lato*, others being upgraded with additions or subtractions into their own families (Webster, 1994) and was validated by the APG II group (Wurdack et al., 2005).

The new classification left family Euphorbiaceae *s.l.* with five subfamilies, 49 tribes, 317 genera and about 8,000 species (Webster, 1994). However, little experimental support met this classification and more studies both in support and against or to further re-organize the family have since been in progress (Bruyns et al., 2006; Davis et al., 2007; Henderson, 1992; Hoffmann and McPherson, 2007; Seigler, 1994; Tokuoka, 2007; Wurdack et al., 2005).

Using recent molecular study results based on DNA sequencing with molecular markers *rbcL*, *atpB*, *matK* and 18S *r*DNA; plastids *RBCL* and *TRNL-F* and a nuclear gene *PHYC* (Tokuoka, 2007; Wurdack et al., 2005), Euphorbiaceae *s.l.* family has recently been split again into five families namely Euphorbiaceae *sensu stricto*, Pandaceae, Phyllanthaceae, Picrodendraceae, and Putranjivaceae (Tokuoka, 2007). Work on re-organization and proof of monophyly within these groups has been going on (Riina et al., 2010; Sierra et al., 2010; Vorontsova and Hoffmann, 2008; Vorontsova et al., 2007; Wurdack and Davis, 2009). According to Stevens (2010), Euphorbiaceae Jussieu *s.s* is now made up of 218 genera and 5,735 species and has been subdivided into four (supported) clades namely Chelosiodeae K. Wurdack and Petra Hoffmann, Acalyphoideae Beilscmeid *s.s*, Crotonoideae Beilschmeid *s.s*, and Euphorbiodeae Beilscmeid *s.s*.

A note on Euphorbiaceae ethnomedicine

Just like the complexity in classification, ethnomedicine of Euphorbiaceae is very diverse. According to Seigler (1994), this diversity is due to the presence of a wide range of unusual secondary metabolites that makes most of the members poisonous. The family hosts one of the most poisonous substances of plant origin that is, ricin, which is a protein found in *Ricinus communis* (Palatnick and Tenenbein, 2000), whereas other species like *Jatropha curcas* L. are reported to be comparatively poisonous (Mampane et al., 1987).

In an attempt to reveal the wide diversity of poisons of the family, Abdel-Fattah (1987) lists examples of species with following features: fish poisons e.g. *Euphorbia scheffleri* Pax, *Euphorbia tirucalli* L., and *Euphorbia inaequilatera* Sond; human poisons: *Euphorbia ledienii* A. Berger, *Euphorbia heterophylla* L., *Euphorbia cooperi* N.E.Br. ex A. Berger, *Euphorbia candelabrum* Kotschy, *Euphorbia virosa* Willd., *Euphorbia poissonii* Pax, *Euphorbia unispina* N.E.Br. and *Euphorbia venenifica* Tremaux ex Kotschy; poisons of domestic animals: *Euphorbia caput-medusae* L., *Euphorbia silenifolia* (Haworth) Sweet, *Euphorbia ingens* E. Mey. Ex Boiss; as well as irritating ones: *E. tirucalli*, *Euphorbia poissonii, Euphorbia unispina* and *E. venenifica*. In addition, some members are said to cause or influence susceptibility to certain body ailments. For example *E. tirucalli, Euphorbia leuconeura*, *J. curcas* and others are known to be co-carcinogenic and can influence/promote excessive cell division resulting in tumour growth (Hirota and Suttajit, 1988; Van Damme, 2001; Vogg et al., 1999). Also latex of *E. tirucalli* and *Euphorbia royleana* is known to cause conjunctivitis on contact with eyes (Shlamovitz et al., 2009; Van Damme, 1989).

However, some members are very useful substances. Since time immemorial, many Euphorbiaceae have been popular traditional medicinal herbs. Genus *Euphorbia* and indeed family Euphorbiaceae were named in honour of a Greek physician to King Juba II of Mauritania called

Euphorbus believed to have used *Euphorbia resinifera* latex to cure ailments for example, when the King had a swollen belly (Lovell, 1998; Van Damme, 2001). As early as 2 BC, Euphorbiaceae such as *Croton oblongifolius* Roxb. and *Croton tiglium* Willd. were used to cure liver diseases, sprains, snake bites, and as a purgative for the first as well as insanity, convulsions, asthma, tumors, rheumatism for the latter, as documented in the Indian Ayurveda medicine system (Kapoor, 1989). Hooper (2002) also reports the use of *Euphorbia polycarpa*, *Euphorbia hirta*, and *Acalypha indica* L. for treatment of different ailments in the ancient Ayurveda system. In ancient Chinese medicine, Lai et al. (2004) report 33 species belonging to 17 genera of Euphorbiaceae used in herbal medicine. Similar reports have been cited for the ancient Yucatan herbal system applying different Euphorbiaceae like *Euphorbia ptercineura* for asthma and cough; *Croton peraeruginosus* for pimples and *Phyllanthus micrandrus* Müll. Arg. for wounds, inflammations and infections among others (Ankli et al., 1999).

Even today, many Euphorbiaceae plant concoctions, fresh latex and teas are used in alternative medicine. For example, *E. tirucalli* is known for its curative features against diseases like warts, cancer, gonorrhea, arthritis, asthma, cough, earache, neuralgia, rheumatism, toothache, excrescences, tumours and others (Cataluna and Rates, 1999; Duke, 1983; Van Damme, 1989). *Euphorbia thymifolia* is used as an anti-viral against simplex virus-2 (Gupta, 2007) whereas *E. maculata* is said to cure cholera, diarrhea and dysentery (www.botanical.com.). The latter website lists a number of Euphorbiaceae with varying curative features including: *Euphorbia. peplus* L., *Euphorbia. peploides*, *Euphorbia pilosa*, *Euphorbia palustris* being remedies for hydrophobia; *Euphorbia peplus, Euphorbia helioscopia*, *Euphorbia humistrata*, *Euphorbia hypericifolia, Euphorbia portulacoides* L., *Euphorbia iata* Engelm, *Euphorbia marginata* Pursh, *Euphorbia drummondii* and *Euphorbia heterodoxa* for general home ailments. Most of the species, however, are cited in folk medicine where their dosage and efficacy are not clear hence the need for medical research to establish their safety.

Research has shown that some Euphorbiaceae are actually potent as medicinal plants and their extracts have been isolated and patented as modern drugs. A table of some US patents is shown in Table 1.

Some of the extracts are registered drugs and as such available on the market. Examples include Euphorbium (resiniferatoxin), from latex of *Euphorbia resinifera* (Appendino and Szallasi, 1997) marketed as 'Complexe Lehning Euphorbium N 88' and used as a nasal spray or compositum against viral infections, rhinitis of various origins, sinusitis, chronic nasal discharge, dry and inflamed nasal membranes as well as flu symptoms. *Euphorbia pilulifera* (the asthma weed) extract has been cited in Steadman's drugs list and can be applied against asthma, coryza and other respiratory infections and as an anti-spasmodic (www.drugs.com). Dysenteral® is an extract from *Euphorbia hirta* and is used in the treatment of diarrheal diseases (Elujoba et al., 2005) while Radix is an extract from *Euphorbia kansui* roots used as a purgative. Many other Euphorbiaceae are prospective important veterinary and agricultural biocides as demonstrated in literature (Table 2).

Other uses of Euphorbiaceae include biodiesel production e.g. *E. tirucalli* (Duke, 1983; Van Damme, 2001), *Euphorbia lathyris* (Duke, 1983); *J. curcas* (Achten et al., 2008; de Oliveira et al., 2009; Kaushik et al., 2007; Kumar and Sharma, 2005); *M. esculenta* (Adeniyi et al., 2007); *R. communis* (Benavides et al., 2007; Meneghetti et al., 2007) among others. Others are sources of food e.g. *M. esculenta* (Aloys and Ming, 2006), starch e.g. *M. esculenta* (Sanchez et al., 2009; Srinivas, 2007), while others are ornamental due to their attractiveness such as *Euphorbia milli, tirucalli* (Van Damme, 1989 and 2001), *Euphorbia obesa* and *Euphorbia pulcherrima.* Other minor uses include production of fuel wood, curving of wooden crafts, use as hedge/fence plants, timber production, use in re-forestation programs and others.

The above account indicates that in addition to other uses mentioned, Euphorbiaceae is an important source of herbal medicine of human, veterinary and agricultural importance. The outstanding question is 'Why is this family significant as a medicinal taxon?' The objective of this review is to attempt to provide an explanation why this may be so.

WHY IS EUPHORBIACEAE RICH IN MEDICINAL COMPOUNDS?

Euphorbiaceae *s.l.* is composed of five subfamilies, 49 tribes, 317 genera and about 8,000 species (Webster, 1994). This makes it one of the biggest plant families with probably the highest species richness in many habitats. The implication is that in absolute terms, there is a higher probability of having more species that are medicinal in that one family as compared to other families. Although such comparison (as to which family has the highest number of medicinal species) may not have been done, it appears that Euphorbiaceae may not compare badly to other families. Cited inventories in different parts of the world reveal that in Kenya, of 900 medicinal species recorded, about 60 belong to Euphorbiaceae (Leakey, 2006), in Loja province (Southern Ecuador) they are 11 species of 214 (Bussmann and Sharon, 2006), in Jinja district (Eastern Uganda) they are 5 out of 88 (Bukenya-Ziraba and Kamoga, 2007), in Sango bay area (Southern Uganda) they are 14 out of 186 (Ssegawa and Kasenene, 2007), in Riau province, Sumatra, Indonesia, they are 11 out of 114 (Grosvenor et al., 1995). This approximates to about 7% of the species cited. Bearing in mind that there are about 350 families in the plant

Table 1. Examples of US patents of medicinal Euphorbiaceae extracts.

Patent no.	Inventor	Claim/ailments	Species involved	Patent date
US 5707631	Advanced plant Pharm. Inc.	Therapeutic herbal composition	*E. lathyris*	January 1998
US 6844013	Peplin Biotech Pyt.	Immuno-stimulation	*E. peplus, E. hirta, E. drummondii*	March 2001
US 2003/0165579 A1	LaRiviere Grubman and Payne LLP.	Tumour inhibition	*E. antiquorum*	February 2002
US 6432452	Peplin Biotech Pty.	Anti-cancer compound	*E. peplus, E. hirta, E. drummondii*	August 2002
US 2003/0171334 A1	Peter Gordon Parsons	Prostate cancer	*E. aaron-rossii, E. tirucalli, E. tomentella, E. tomentosa*	September 2003
US 6923993	Nicholas Dodato	Anti-cancer components	*E. obesa*	August 2005
US 2007/0248694 A1	PhytoMyco Research Corp.	Anti-inflammatory properties	*E. hirta*	October 2007
US 2006/0198905 A1	Rajesh Jain and others	Ano-rectal and colonal diseases	*E. prostrata*	May 2008

Source: United States Patent and trademark office (seen at http://patft.uspto.gov.)

Table 2. Examples of pesticidal species in Euphorbiaceae and their remedies.

Pesticidal feature	Species	Chemical compound(s)	Cited reference(s)
Anti- bacterial	*E. guyoniana* Boiss. and Reut.	Diterpenes	El-Bassuony (2007)
	E. sororia Schrenk	Ceramides and ellagic acid derivatives	Zhang et al. (2008)
	E. hirta	Tannins, alkaloids and flavonoids	Ogbulie et al. (2007)
	E. pubescens Vahl.	Diterpenes and ent-abietanes	Valente et al. (2004)
	M. esculenta	Glycocide	Zakaria et al. (2006)
	E. sessiliflora Roxb.	Triterpenes and ellagic acid derivatives	Sutthivaiyakit et al. (2000)
	E. segetalis L.	Coumarins and steroids	Madureiira et al. (2002)
	J. podagrica Hook.	Diterpenoids	Alyelaagbe et al. (2007)
	E. ebracteolata Hayata	Casbane diterpenoids	Xu et al. (1998)
	E. heterophylla	Saponins, flavonoids and tannins	Falodun et al. (2008)
	Drypetes inaequalis Hutch.	Triterpenoid esters and saponins	Awanchiri et al. (2009)
Anti-viral	*E. kansui*	Triterpenes, sterols and diterpenes	Zheng et al. (1998)
	E. hyberna L.	Diterpenes	Bedoya et al. (2009)
	E. cotinifolia L. , *E. tirucalli*	Diterpenes	Bentacur-Galvis et al. (2002)
	E. thymifolia	Alkaloids	Jabbar and Khan (1965)
	E. thymifolia	Triterpenes and alkaloids	Lin et al. (2002)

Table 2. Contd.

Anti-fungal	*Macaranga monandra* Müll.Arg.	Diterpenes	Salah et al. (2003)
	E. nivulia Buch.-Ham.	-	Annapurna et al. (2004)
	E. hirta, E. tirucalli	Diterpenes and triterpenes	Mohamed et al. (1996)
	R. communis	Fatty acids	Maria Fatima et al. (2004)
	J. curcas	Glucanase protein	Wei et al. (2005)
Nematicidal	*E. tirucalli*, *E. helioscopia*, *E. splendens* Bojer. Ex Hooke. *E. pulcherrima* Willd. Ex Klotzsch.	Diterpenes	Devi and Gupta (2000)
	E. pulcherrima	-	Cox et al. (2006)
	Phyllanthus niruri L.	Flavanones	Shakil et al. (2006); Shakil et al. (2008)
	E. kansui	Diterpenes and ingenane	Shi et al. (2007); Shi et al. (2008)
	E. hirta	Phenols	Adedapo et al. (2005)
	J. podagrica	Peptides	Dahiya (2008)
Moluscicidal	*E. tirucalli*	-	Jurberg et al. (1985); Vassiliades (1984)
	E. conspicua N.E. Br.	Diterpenes and triterpenes	Dos Santos et al. (2007)
	E. splendens	-	de Vasconcellos and de Amorim (2003)
	J. elliptica Müll. Arg.	Diterpenes	dos Santos and Sant'Ana (1999)
	J. curcas	Phorbal esters	Gubitz et al. (1999)
	E. paralias L.	Diterpenes	Abdelgaleil et al. (2002)
Insecticidal	*E. hirta*	Flavonol glycosides	Liu et al. (2007)
	J. curcas	Sterols, triterpenes alcohols and acids	Adebowale and Adedire (2006)
	R. communis	Flavonoids	Shripad (2003)
	R. communis	Ricinine	Maria Fatima et al. (2004)
	J. curcas	Diterpenoids	Goel et al. (2007)
	C. pseudoniveus, C. suberosus	Essential oils	Perez-Amador et al. (2003)
Anti-leishmanial	*D. chevalieri*	Furansesquiterpene and triterpenoids	Wansi et al. (2007)
	J. grossidentata, J. isabellii	diterpenes	Schmeda-Hirschmann et al. (1996)
	J. grossidentata	Diterpenes	Akendengue et al. (1999)
	P. cajucara	Essential oils	Ahmed et al. (2006)

Kingdom, this is not a bad score. This, however, depends upon the region in question since Euphorbiaceae is most prevalent in tropical and subtropical areas.

According to Oldfield (1997), a good number of Euphorbiaceae species especially of genus *Euphorbia* (650 species), are succulent. The latter author describes succulence as a plant characteristic mainly tropical or subtropical that has to conserve water due to habitat aridity. Von Willert et al. (1990) describe it as a characteristic that makes a plant temporarily independent from external water supply when soil water conditions have deteriorated such that the roots are no longer able to provide the necessary water from the soil. They argue that this is only a temporary adaptation to aridity and

unless conditions allow the refilling of the plant's succulent tissues, it will not survive. This implies that such plants tend to avoid mechanisms that result into water loss (including thin leaf surface, broad leaves and a large number of leaves), whereas they invest in features that conserve water such as thick waxy leaves, scaly leaves or thorns, fewer/sunken stomata, use of stems for photosynthesis, use of Crassulacean Acid Metabolism (CAM) and others. It is therefore a survival strategy for plants in arid and semi-arid areas.

According to Griffiths et al. (2008), leaf succulence is a key morphological correlate of the capacity for CAM, since succulence increases the plants' commitment to the use of CAM pathway during carbon dioxide fixation. In their experiments with two succulent plants, the latter authors found out that the magnitude of CAM was higher for the more succulent leaves of *Kalanchoe daigremontiana* Raym. Hamet and H. Perrier (Crassulaceae) compared to the less succulent leaves of *Kalanchoe pinnata* (Lam.) Pers. In the same spirit, Van Damme (1989) had earlier on pointed to the CAM-succulence syndrome stating that the two have to always go together, to which Lüttge (2004) concurs insisting that all CAM plants display some level of succulence.

The CAM pathway is known to be under circadian control and is subject to regulation by multiple oscillators, which modulate elements of the pathway in line with environmental conditions (Borland et al., 1999; Borland and Taybi, 2004). In line with this, Lüttge (2004 and 2008) enumerates a 'wealth of environmental factors' known to determine, or at least modulate the expression of CAM to include: carbon dioxide, water, absolute temperatures, day-night temperature regimes, irradiance and salinity among others.

The latter author goes on to provide a model that relates these factors, drawing a conclusion that CAM-prone ecosystems are those that are governed by a network of interacting stress factors requiring versatile responses and not systems where a single stress factor strongly prevails. They point out a number of CAM domains or ecosystems that are likely to host CAM/succulent plants including submerged aquatic sites, deserts, salinas, savannahs, inselbergs, forests, and high latitudes such as tropical highlands and alpine regions. This implies that although the CAM pathway is an adaptation for succulent plants to balancing their carbon and water budgets (Lüttge, 2008; Von Willert et al., 1990), it is also a survival mechanism for adverse conditions. Indeed, the extent of succulence has been positively correlated to both colonization of increasingly arid habitats and an increased contribution of CAM activity to total carbon gain (Herrera, 2009; Kluge et al., 2001, Van Damme, 1989 and 2001), implying that succulent plants are better equipped for new habitat colonization than their non- or less succulent relatives, which gives them higher chances for survival in a wider habitat range.

As an extra adaptation, some succulent plants have been found to combine both C3 and CAM pathways. For example, Van Damme (1989 and 2001) reports that *E. tirucalli* utilizes both pathways. Its minute deciduous leaves utilize the C3 pathway while the stem uses CAM. He explains that the small leaves are preferentially used in normal situations whereas the green stem takes over when the leaves fall off in arid conditions. According to him, a combination of both pathways increases the plant's water use efficiency (WUE) since the small leaves have a high affinity for carbon dioxide but tend to use water less efficiently. He predicts that there could be many other Euphorbiaceae using the same mechanism which he says improves productivity and ability to colonize a wide range of habitats.

Euphorbiaceae are very widely distributed in almost all habitats and occupy a wide range of climatic and soil disparities. Ahmad et al. (2006) and Bloomquist (2004) report that different habitat conditions e.g. soils, pH, temperatures and moisture tend to influence plant physiological processes hence the manufacture and accumulation of different chemical substances. In agreement, Melten et al. (2009) confirm that plants' responses can differ due to different factors. For example, physiological alteration of photosynthetic enzyme ratios to adjust to changing light conditions, suberin production to limit moisture loss from roots, genetic regulation of enzymes in response to resource limitation, or production of secondary metabolites in leaves in response to insect/microbial attack. In the same view, Veronese et al. (2003) found out that different herbivores (as found in different environments) tend to induce action of different defense systems. The implication of all this is that due to a wide range of conditions, which different Euphorbiaceae species are subjected to, the latter tend to manufacture a wide range of secondary plant substances to aid response to a disparity of stimuli in their particular habitats. For example, Zhang et al. (2000) reported manufacture of different lectins due to different environmental stress factors that occur in varying habitats. Lectins constitute part of a plant's defense system against herbivores (Van Damme, 2008). Similarly, Agrawal and Rutter (1998) found that changes in environmental cues can trigger modifications in a plant's defense strategy as was witnessed in ant plants (*Myrmecodia* spp.). Also, Taniguchi et al. (2002) established that production of secondary substances like pentagalloylglucose was remarkably enhanced under light irradiation compared to dark conditions while tannin production was greatly affected by changing the concentrations and composition of nitrogen sources. These and other findings support the view that Euphorbiaceae may have a variety of medicinal substances due to a disparity of environmental conditions (stress factors) accruing from a wide habitat range.

Biosynthesis of secondary metabolites is a complex process and is still poorly understood. Hadacek (2002)

states that biosynthesis and accumulation of secondary metabolites arise from highly regulated processes requiring both genetic and environment-specific controls. In a related view, Cavalier-Smith (2007) says that secondary metabolites are produced from universally present precursors mostly acetyl-CoA, amino acids or shikimate (shikimic acid) by taxon specific enzymes – the reason why most secondary metabolites are restricted to a single major taxon on the universal phyllogenetic tree or evolutionally related taxa. This specificity has been shown and supported by modern molecular techniques, for example, using cytochrome P450 enzymes (CPY79A1 and CYP71E1) involved in biosynthesis of the cynogenic glucoside dhurrin in *Sorghum bicolor* L. (Kahn et al., 1999). This phenomenon is not new in the plant kingdom because some secondary metabolites are considered to be so taxon specific as to be used in classification of certain taxa or acting as proof of monophylly (Gershenzon and Mabry, 1983; Herbert, 1989; Seigler, 1994; Wink, 2003). What may be controversial, however, is that there is a growing volume of evidence to show that plants of the same genus or family may synthesize different or at least varying secondary metabolites when growing in different conditions (Figueiredo et al., 2008; Koricheva et al., 1998; Wink, 2003). Such inconsistencies in secondary metabolite profiles have been attributed to among other factors, differential expression of corresponding genes (Wink, 2003) but also change in gene sequence and mutations (Theis and Lerdau, 2003). These genetically related factors act in the wake of varying environmental factors, to cause alterations in secondary metabolite assemblages reflecting adaptations and particular life strategies embedded in a given phylogenetic framework (Koricheva et al., 1998). As indicated by Ogunwenmo et al. (2007), this argument appears plausible for the case of widely distributed families like Euphorbiaceae. Varying secondary metabolites may be synthesized within the taxon, as a result of different gene expression and increasing mutation loads, accruing from stressful environments that characterize most Euphorbiaceae habitats. This may result into a richer assemblage of secondary metabolites within the family.

During their evolution, CAM plants have developed a number of anatomical, physiological and genetic changes/adaptations, which differentiate them from C3 plants. Cushman and Bohnert (1997) mention several of them such as thin-walled cells containing prominent vacuoles, varying degrees of succulence and capacity to handle high degrees of organic acid accumulation. The latter authors go on to say that just like evolution processes, CAM induction or process of shifting from C3 to CAM, involves the regulation of a variety of enzymes and metabolite transporters making it a very complex metabolic adaptation (to environmental stress). They give an example of increased activities of glycolytic, gluconeogenic and C4 acid metabolism enzymes including phosphoenolpyruvate carboxylase (PEPC), phosphoenolpyruvate carboxykinase (PEPCK) and pyruvate phosphate dikinase (PPDK) which increase 40 fold due to environmental stress. On the genetic side, the same authors, citing transcription essays with nuclei isolated from leaves of *Mesembryanthemum crystallinum* L. (Aizoaceae), show that CAM-specific genes increase two to six times when plants are exposed to high salinity (a stress factor). In support, Borland and Taybi (2004), note that although physiological processes associated with this high organic acid accumulation are energy-intensive, the potential for high productivity is not compromised. To substantiate this fact, they give examples of agronomically important CAM species including pineapple (*Ananas comosus* Mill.) and *Agave* spp. that show productivities rivaling that of C3 and C4 plants. Since organic acids and genes are responsible for physiological plant processes, this implies that CAM plants are likely to have higher productivity both in quantity and quality (variety) of chemical substances including enzymes, proteins, amino acid as well as secondary metabolites of various nature.

Possession of a variety of chemical substances may entail being rich in medicinal attributes. For example, over sixty jatrophane, modified jatrophane, segetane, pepluane and paraliane diterpenoids were extracted, purified and characterized from different Euphorbiaceae such as *Euphorbia dendroides*, *Euphorbia characias*, *Euphorbia peplus*, *Euphorbia amygdaloides*, and *Euphorbia paralias*. Based on jatrophane and modified jatrophane skeletons these were shown to be potent inhibitors of P-glycoprotein activity – a membrane protein that confers upon cells the ability to resist lethal doses of certain cytotoxic drugs by pumping them out of the cells, thus reducing cytotoxic effects (Barile et al., 2008). Similarly, Corea et al. (2005) report the discovery of two new diterpenes, pepluanone 1 and 2 from *E. peplus*, which act as anti-inflammatory agents. Also Falodun et al. (2008) identified secondary metabolites such as saponins, flavonoids and tannins from *E. heterophylla* which exhibited good activity against xanthine oxidase enzymes. Related findings are distributed in the whole Euphorbiaceae literature (Table 3).

CONCLUSION

Each plant family may have its own good reason for possession of medicinal properties. For Euphorbiaceae family members, it would appear that their diverse medicinal properties are associated with their wide distribution which is supported by their survival adaptations such as succulence and CAM pathway. The exposure to a wide range of habitats predisposes them to inevitably high mutation loads (accruing from stressful habitats) and a large range of environmental stimuli hence the necessity to develop a wide battery range of defensive secondary metabolites. These issues may explain why the family is widely pharmaceutical. These

Table 3. Chemical substances found in Euphorbiaceae and their pharmaceutical indications.

Chemical substance	Medicinal indication	Cited reference(s)
Diterpenes	Anti-tumor	Duarte et al. (2008); Konoshima et al. (2001); Krebs et al. (2004)
	Anti-biotic	El-Bassuony (2007); Li et al. (2008); Mathabe et al. (2008)
	Anti-fungal	Salah et al. (2003)
	Anti-plasmodial	Attioua et al. (2007)
	Anti-ulcergenic	Hiruma-Lima et al. (2002)
	Trypanacidal	Schmeda-Hirschmann et al. (1996)
Triterpenes	Anti-biotic	Awanchiri et al. (2009); Mathabe et al. (2008)
	Vaso-depressor	Barla et al. (2006)
	Anti-inflammatory	Canelon et al. (2008); Nkeh et al. (2008)
	Analgesic	Nkeh et al. (2003)
	Anti-fungi	Ekpo and Pretorius (2007)
Flavonoids	Anti-malarial	Liu et al. (2007)
	Anti-inflammatory	Ekpo and Pretorius (2007)
Saponins	Cytotoxic	Kiem et al. (2009)
	Anti-ulcer	Ukwe (1997)
Tannins	Anti-septic	Ekpo and Pretorius (2007)
	Anti-viral	Bessong et al. (2006); Liu et al. (1999)
	Anti-mutagenic	Rossi et al. (2003)
	Anti-fungal	Hwang et al. (2001)
Alkaloids	Anti-microbial	Dias et al. (2007); Gressler et al. (2008)
	Anti-tumor	Suarez et al. (2004)
Esters	Anti-tumor	Blanco-Molina et al. (2001); Goel et al. (2007)
	Anti-biotic	Goel et al. (2007)
	Cytotoxic	Baloch et al. (2006)
	Allergic reactions	Thumm et al. (2002)
	Cancerous	Cataluña and Rates (1999)
Ricin	Cytotoxic	Lombard et al. (2001)
	Lipolytic	Lombard et al. (2001)
	Invertase activation	Vattuone et al. (1991)
Phenols	Anti-tumor	Yu et al. (2005)
	Anti-oxidant	Yang et al. (2007)

literature review findings compare well with reports of other workers like Ahmad et al. (2006) and Okgibo et al. (2009) who similarly but independently reviewed a variety of Euphorbiaceae-based phytochemi-cals including alkaloids, phenols, flavonoids, saponins, tannins and essential oils and described their origins, characteristics and therapeutic uses.

This review has revealed a rich variety of medicinal and potentially medicinal properties of Euphorbiaceae and attempted to elucidate why Euphorbiaceae tick as medicinal plants. Euphorbiaceae is therefore, a good starting point for a search for phytomedicines of human, veterinary or pesticidal nature.

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