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Review

Piper umbellatum L.: A comparative cross-cultural analysis of its medicinal uses and an ethnopharmacological evaluation

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ABSTRACT

Aim of the study: This review assesses the botany, traditional medicinal uses, phytochemistry, pharmacology and toxicology of *P. umbellatum*.
Materials and methods: Information on *P. umbellatum* was gathered via the internet (using Scirus, Google Scholar, CAB-Abstracts, MedlinePlus, Embase, Scielo, and Web of Science) and libraries. Additionally, previously unpublished work on the traditional uses of *P. umbellatum* from our National Study of the Medicinal Plants of the Dominican Republic has been included.
Results: Piper umbellatum is a Neotropical plant species widely distributed in Mexico, Central America, South America and the West Indian Islands. It has also been introduced to Africa and South-East Asia. Traditional uses for this plant are recorded in 24 countries in three continents, America, Africa and Asia for a wide range of ailments such as kidney, women diseases, diarrhea, skin affections, burns, rheumatism, malaria, intestinal parasites, inflammation and fever. We have analyzed the cross-cultural agreement among traditional uses in different countries and found a high degree of consensus for the indications kidney/diuretic, stomachache and wounds. Phytochemical studies of *P. umbellatum* have demonstrated the presence of terpenes (mainly found in the essential oil), alkaloids, flavonoids, sterols and other classes of secondary metabolites. The extracts and pure compounds derived from *P. umbellatum* show a wide spectrum of pharmacological activities including antibacterial, anti-inflammatory, analgesic, antioxidant, cytotoxic, antimalarial, antileishmanial, and antitrypanosomal activity. A first commercial product is in development, based on the plant's protective characteristics against UV irradiation.
Conclusions: The interesting biological activities of *P. umbellatum* need further research in *in vivo* experiments and clinical studies. The outcome of these investigations will determine the possible development of drugs from *P. umbellatum*.

Contents

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1. Introduction

Since 1978, the World Health Organization has promoted the development of Primary Health Care (PHC) and the importance of the involvement of traditional health care systems, including the use of medicinal plants (Anonymous, 1979, 1988; WHO, 1978). Several authors have described ways in which medicinal plants could be a part of PHC (Farnsworth et al., 1985; Le Grand and Sri-Ngernyuang, 1989; Wondergem et al., 1989). Our own experience in Peru and the Dominican Republic has demonstrated that PHC will fail if traditional medicine, including medicinal plants, is not taken into account (Hoogte and Roersch, 1984, 1988; Roersch, 1994; Roersch and Hoogte, 1987).

In the Dominican Republic, two medical systems can be distinguished: the formal medical system and the informal medical system. The formal medical system is based on the Western conventional medical system (in which the biomedical model predominates) and involves hospitals, clinics, drugstores, insurance companies and teaching facilities (universities). The informal medical system can also be called the Traditional Dominican Health System (TDHS), which is based on ancient concepts and practices in the Dominican culture. These concepts and practices have several origins, including the slaves, who contributed a polytheistic African cosmology (Deive, 1981, 1992); the Spaniards, with their medieval cosmology, including spiritualism and alchemy (Kuschick, 1995); and elements of the Taina culture (the original inhabitants of the island) (Davis, 1987). Locally, the following terms are used: 'medicina de farmacia' ('drugstore medicine') for the formal health system and 'plantas ('matas') de la tierra' ('plants of the earth') for the informal health system (Roersch, 1995). Medicinal plants play an important role in the Traditional Dominican Health System. Medicinal plants and other ingredients of this traditional medical system are offered at local markets, on street corners and in special stores (boticas). In a study concerning the market for medicinal plants, we found that in the capital, Santo Domingo, the annual sales total for medicinal plants amounts to $702,000 USD (Roersch, 1999). Publications about the use of medicinal plants in the Dominican Republic are not abundant, and most are descriptions of popular uses (Cordero, 1986; IMD et al., 1994a,b,c, 1997, 1999a,b,c,d; Liogier, 1990; Mañon et al., 1992; Peguero, 2002; Peguero et al., 2001; Polanco et al., 1998); some include experimental data (phytochemistry and biological characteristics) (Bonnelly et al., 1985; Germosén-Robineau, 1995). Recently, studies have been undertaken to determine the relation between the uses of medicinal plants by Dominican immigrants in New York and their country of origin (Ososki et al., 2007; Reiff et al., 2003; Vandebroek et al., 2007). However, there has been no extensive, systematic research on the use of medicinal plants in the Dominican Republic. For the integration of medicinal plants in the official health system and for the development of a national policy on alternative and complementary health practices, it will be necessary to have a broad knowledge of the uses of the medicinal plants within the TDHS. As stated by the WHO (WHO, 2002), it is necessary for a country with an active traditional health system, to formulate a national health care policy, to have a broad knowledge of traditional health practices. Therefore, the Instituto de Medicina Dominicana (IMD, or the Dominican Institute of Medicine) formulated a project for this purpose, calling it the National Study of the Medicinal Plants of the Dominican Republic. In 2000, together with the Pan-American Health Organization (PAHO), a questionnaire was developed. With the help of students from the Universidad Nacional Pedro Henriquez Ureña (UNPHU), we have thus far conducted more than 5000 interviews with about 1000 persons in each of the provinces of the Dominican Republic. With the outcome of these interviews, an ethnopharmacological database has been constructed. *P. umbellatum* appears to be an important plant in the treatment of, among other conditions, leucorrhoea, locally known as 'vaginal flow'. This disorder is very common in the Dominican Republic. A first step in the validation of this ethnopharmacological application is the assessment of the existing literature on this plant. The presented review is the result of this process and includes previously unpublished work.

2. Botany

Piper umbellatum L. (Piperaceae, syn. based on Tropicos: *Pothomorphe umbellata* (L.) Miq., *Lepianthes umbellata* (L.) Raf., *Heckeria umbellata* (L.) Kunth., *Peperomia umbellata* (L.) Kunth) is a perennial scrambling shrub or woody herb, 1–2.5(−4) m tall. Stems numerous, succulent, ribbed, forming a dense clump, rooting at the nodes, main roots woody. Leaves alternate, almost circular to reniform, 5–40 cm × 5–40 cm, blade dark green above, grayish below, base deeply cordate, apex shortly acuminate to rounded, margins entire or crenulate, sparsely to densely hairy on the veins on both sides, venation palmate, 11–15 veins, petiole 6.5–30 cm long, dilated and sheathing basally. Inflorescence 5.5–15 cm long, 2–8 together in false umbels, peduncle 3–12 cm long, 1–3 peduncles together, peduncular bracts narrow, 6–8 mm long, white, soon falling. Flowers small, bisexual; floral bracts triangular to rounded, 0.5–0.8 mm wide, subpeltate, margins fimbriate, white, cream or yellow; perianth absent; stamens 2; ovary superior, 1-locular, stigmas 3. Fruit a drupe, obpyramidal, 3-angled, 0.6–1 mm × 0.4–0.6 mm, brownish seed globose (Schmelzer, 2001).

This is a Neotropical species widely distributed in Mexico, Central America, South America and the West Indian islands. It has been introduced to Africa and South-East Asia and is now broadly naturalized (Domis and Oyen, 2008; Liogier, 2000; Saralegui, 2004; Schmelzer, 2001).

3. Traditional medicinal uses of *P. umbellatum* in a cross-cultural context

Besides the medicinal uses of *P. umbellatum*, the plant is also used in medical-magic rituals in Cameroon (Agbor et al., 2005) and Gabon (Akendengue and Louis, 1994). It is also used in Gabon as a fetish to cause compassion (Domis and Oyen, 2008), to change the sex of a child at birth in Cameroon (Jiofack et al., 2008), in religious affairs in Brazil (Azevedo and Silva, 2006), as a fragrance against 'mal aire' (bad air) in Ecuador (Pohle and Reinhardt, 2004) and in Ghana as bait to attract fish (Domis and Oyen, 2008). In the Dominican Republic, the leaves are used by farmers to protect themselves against the heat by putting the leaves under their hats. In many countries, *P. umbellatum* is used as a vegetable or condiment (young leaves and inflorescences eaten raw, boiled or steamed) in people's daily diets. In tropical Asia, the fruits are eaten as a delicacy (Schmelzer, 2001). The Shuar in Ecuador use it as a condiment (Pohle and Reinhardt, 2004). The nutritional values and mineral contents of *P. umbellatum* (leaves) are as follows: ascorbic acid: 181 mg/100 g DM, carbohydrates: 3.8 g/100 g DM, protein: 3.9 g/100 g DM, moisture: 80% fiber: 2.2 g/100 g DM; and minerals: Ca: 2.36, K: 4.1, Mg: 0.88, Na: 0.12, Fe: 0.05 mg/100 g) (Mensah et al., 2008).

In general, traditional, local uses of medicinal plants are the starting point for the development of new drugs from the same plants (Farnsworth et al., 1985; Farnsworth and Loub, 1983). Numerous ethnopharmacological studies have been performed all over the world in different cultures (Heinrich et al., 2009). To determine the effectiveness of medicinal plants, Trotter and Logan (1986) proposed a method known as the Informant Consensus. They argued that within and between cultural groups plants with scientifically (i.e., pharmacologically) proven effectiveness are more likely to be found, and will have a consistent pattern of usage. Moerman (2007) stated that "consensus will identify plants with significant and appropriate pharmacological properties". This in turn leads to the hypothesis that the same (or consensus) uses of a plant in different cultures should have a scientific basis. We have examined this cross-cultural agreement in the case of *P. umbellatum*.

The medicinal uses of *P. umbellatum* in traditional medicine health systems are recorded in 24 countries across three continents. In Table 1 , these uses are ordered according to the disease classification used in the modern Western biomedical system (Anonymous, 2007). It was necessary to extend this classification with categories such as *Women diseases*, *Liver* and *Fever*, which are used in various traditional medicine health systems. A total of 94 traditional medicinal uses for *P. umbellatum* are registered. In the American continent information has been found for Brazil, Mexico, Jamaica, Cuba, Dominican Republic, Haiti, Costa Rica, French Guyana and Venezuela; in Africa, information was found for Nigeria, Cameroon, Ivory Coast, Gabon, Zimbabwe, Liberia, Congo, Guinea, São Tomé and Príncipe, Burundi, Comoros Islands, Guinea Equatorial and Ghana; and in Asia, the Philippines and Malaysia are mentioned. There are also references to the West Indies, to Africa as a whole, and to East Africa, Central Africa, Southeast Asia and Indochina. In this review, they will be considered a country. The country with by far the most indications is Brazil (35), which also has the largest number of authors (21). In the majority of these countries, literature on this subject has just one author (14). In Asia, one author published a monograph on *P. umbellatum* within the PROSEA project for Southeast Asia (Schmelzer, 2001). A similar project, called PROTA, exists in Africa; in it, Domis and Oyen elaborated on a monograph on *P. umbellatum* (Domis and Oyen, 2008). In the case of the Dominican Republic, our own data, collected in our National Study, are added.

We have distinguished 13 categories of illnesses. The first one, *Urinary tract*, has only two groups of traditional treatments, diuretic and kidneys, but they are present in nine countries in three continents. The majority of the traditional uses in the category of *Women Diseases* have their origin in Africa. Only leucorrhoea, accelerated labor and emmenagogue are also treatments in the American continent. In the *Digestive tract* we see the same pattern as in *Women Diseases* with the exception that two traditional uses are also mentioned in Asia, while in *Women Diseases* no application is found in Asia. In *Skin* the three continents are present, with Asia only represented by one indication, abscesses. In the *Respiratory tract*, America is represented by four treatments and four countries, Africa with two indications and one country and Asia with just one indication and one country. *Liver* is mentioned by 10 authors for Brazil. *Fever* (and sudorific and febrifuge) is mentioned for Brazil, Gabon and Africa. Eight different traditional treatments for *Pain* are recorded in nine countries in two continents (if we include stomachache, up to 13 countries in three continents). The plant is used as an anti-inflammatory in Brazil, Mexico and Cuba and for inflamed tumors in Africa. Also important are the *Wound* healing properties. This category is found in six countries in the three continents. The category of *Swellings*, *contusions* is found in the three continents. These last two more or less related categories have 11 diseases indications combined (including *inflammation* increases this number to 14). *Rheumatism* is mentioned in Africa and the West Indies.

From the 94 medicinal uses, 59 are uses for just one country in one continent; 10 are uses for two or more countries in one continent, 21 are uses for two or more countries in two continents and four are uses for four or more countries in three continents. In Fig. 1, the traditional medicinal uses that occur in two or more countries in one or more continents are ordered. *Women diseases* are represented by four traditional uses out of a total of 14 (Table 1); the *Digestive tract* has three uses out of 17, *Skin* has three uses out of six, *Pain* has four uses out of eight, the group *Inflammation, Wounds* and *Swellings*, *contusions* has six out of 14 and *Urinary tract* has two out of two. The cross-cultural uses with most consensus are kidneys, diuretic, stomachache and wounds. These traditional medicinal uses are present in more than four countries in three continents. These uses, together with the categories *Pain* (with stomachache used in three continents), *Inflammation*, *Wounds*, *Swellings*, *Contusions* (with wounds used in three continents) and *Skin* (with three out of six disease indications mentioned in five countries in two continents), can be categorized as highly indicated for further investigation.

4. Phytochemistry

Phytochemical studies of *P. umbellatum* have demonstrated the presence of terpenes (mainly found in the essential oil), alkaloids, flavonoids, sterols and other classes of secondary metabolites. A catechol, 4-nerolidylcatechol (Fig. 2), is considered the main bioactive compound. It is found in the whole plant (Bergamo et al., 2005; De Oliveira and Akisue, 1984; Desmarchelier et al., 1997; Kijjoa et al., 1980; Núñez et al., 2005; Tabopda et al., 2008; Viana et al., 2000). From the branches, Tabopda et al. (2008) isolated some interesting new bioactive alkaloids, which they named piperumbellactams A–D (Fig. 2). Another bioactive alkaloid, *N*-benzoylmescaline, was found by Isobe et al. (2002) in the aerial parts of a Brazilian *P. umbellatum* (Table 2).

Various studies have analyzed the composition of the essential oil of the leaves of *P. umbellatum*. Three studies were carried out in Brazil, one in Costa Rica, one in Cuba and one in São Tomé and Príncipe. Another study was done in Cameroon, and it detected the presence of cadinene, caryophyllene and phellandrene (Chartol, 1964). This study is not included because the oil was extracted from the leaves and flowers, while the other studies only used the leaves. As one can see in Table 3, there are considerable differences between the presented essential oils. Most striking is the contrast between the essential oil from Africa and the essential oils from the American continent. In São Tomé and Príncipe, the main constituents are the monoterpenoids α- and β-pinene, while in Brazil, Cuba and Costa Rica the sesquiterpenoids β-caryophyllene and germacrene D are the important elements. Within the American continent a salient feature is the singularity of the essential oil of Cuba, where one component, safrole, is most significant (48.7%). The essential oil of Costa Rica has (*E*,*E*)-α-farnesene as one of the three main constituents. This compound is only mentioned by Martins et al. (1998) in São Tomé and Príncipe. Mesquita et al. (2005) present two series of data. One concerns a sample collected in 1999 and the other one in 2001, both in the 'Parque Estadual do Rio Doce' in the state of Minas Gerais. The main components are present in both samples, but the percentages are not the same. Principal differences are in the presence of germacrene D and *trans*-dihydroagarofurane. The last component was not even detected in the sample of 2001! The recently elucidated role played by β-caryophellene to produce anti-inflammatory effects (Gertsch et al., 2008) and the traditional uses of *P. umbellatum* related to inflammation (Table 1) deserve more investigation. The presented differences in the contents of the essential oils of *P. umbellatum* make it very clear that for further comparison of experimental data,

Table 1
Cross-cultural medicinal uses of *P. umbellatum*.

Medicinal use	Part used	Application*	Country	References
Urinary tract				
Diuretic	Not specified	Not specified	Brazil	Britto et al. (2007)
	Root	Not specified	Brazil	Brandão et al. (2008), Hegnauer (1969)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
	Bark	Decoction	Brazil	Schultes (1980), in Hammer and Johns (1993)
	Leaf	Infusion	Cuba	Pino et al. (2005)
	Leaf, root	Not specified	Dominican Republic	Liogier (2000)
	Leaf, root	Not specified	Haiti	Liogier (2000)
	Fruit	Not specified	Nigeria	Ndukwu and Ben-Nwadibia (in press)
	Leaf	Juice	Africa	Domis and Oyen (2008)
	Leaf	Decoction	South-East Asia	Schmelzer (2001)
Kidneys	Inflorescence	Decoction	Brazil	Agra et al. (2007)
	Leaf	Decoction or infusion	Brazil	Santos and Lima (2008)
	Root	Not specified	Brazil	Rodrigues and Guedes (2006)
	Leaf	Decoction	Africa	Domis and Oyen (2008)
	Leaf	Maceration	Cameroon	Chartol (1964)
	Leaf and fruit	Not specified	Indochina	Schmelzer (2001)
	Leaf or root	Decoction	Dominican Republic	Roersch**
Women diseases				
Emmenagogue	Not specified	Decoction	Ivory Coast	Bouquet and Debray (1974), in Hammer and Johns (1993)
	Aerial parts	Not specified	Ivory Coast	Schmelzer (2001)
	Leaf	Juice	Africa	Domis and Oyen (2008)
	Leaf	Juice	Brazil	Roig (1945)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
Anti–abortive	Whole plant	Decoction	Ivory Coast	Bouquet and Debray (1974), in Hammer and Johns (1993)
	Aerial parts	Not specified	Ivory Coast	Schmelzer (2001), Domis and Oyen (2008)
	Aerial parts	Not specified	Central Africa	Schmelzer (2001), Domis and Oyen (2008)
	Not specified	Not specified	Gabon	Bodinga-bwa-Bodinga and Van der Veen (1993)
Women diseases	Leaf	Decoction	Guinea	Vasileva (1969), in Hammer and Johns (1993)
Pain and abundant bleeding during menstruation	Leaf	Maceration	Cameroon	Noumi et al. (1999)
Antihemorrhagic	Aerial parts	Not specified	Ivory Coast	Schmelzer (2001)
Painful menstruation	Leaf	Maceration	Cameroon	Noumi and Yomi (2001)
Menstruation	Leaf or root	Not specified	Africa	Domis and Oyen (2008)
Accelerate labor	Not specified	Decoction	Mexico	Browner (1985)
Calms birth pains	Flower, leaf	Decoction	Cameroon	Jiofack et al. (2008)
Expulsion of the placenta	Root (with *Hyptis pectinata*)	Decoction	Ivory Coast	Kerharo et al. (1950)
To clean the belly of women after giving birth	Leaf	Juice, as an enema	Zimbabwe	Yamada (1999)
Galactogogue	Leaf	Juice	Africa	Domis and Oyen (2008)
Leucorrhoea	Leaf or root	Decoction	Africa	Domis and Oyen (2008)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
Vaginal flow	Leaf (with roots of *Agave* sp., leaves of *Momordica charantia* and *Argemone mexicana*)	Decoction	Dominican Republic	Roersch**
	Leaf	Infusion	Dominican Republic	Roersch**
	Leaf (with leaves of *Momordica charantia*)	Decoction	Dominican Republic	Roersch**
Digestive tract				
Diarrhea	Root	Maceration and drunk with white wine	Brazil	Hammer and Johns (1993)
	Leaf	Poultice, external	Mexico	Browner (1985)
Digestive	Root	Decoction	Africa	Domis and Oyen (2008)
Dyspepsia	Root	Decoction	Africa	Domis and Oyen (2008)
Constipation	Root	Decoction	Africa	Domis and Oyen (2008)
Dysentery	Leaf	Maceration (with juice of old banana spike)	Cameroon	Noumi and Yomi (2001)
Peptic ulcer	Leaf	Maceration	Cameroon	Noumi and Dibakto (2000)

Table 1 (*Continued*)

Medicinal use	Part used	Application*	Country	References
Laxative for pregnant women	Not specified	Decoction	Guinea	Vasileva (1969), in Hammer and Johns (1993)
	Leaves with palm kernel oil	Boiled with local palm kernel oil	Nigeria	Ndukwu and Ben-Nwadibia (in press)
Edema (stomach)	Leaf	Tied on the stomach	South-East Asia	Schmelzer (2001)
Intestinal parasites	Leaf	Maceration	Cameroon	Noumi and Dibakto (2000)
	Leaf	Not specified	Central Africa	Domis and Oyen (2008)
	Leaf	Not specified	Congo	Domis and Oyen (2008)
	Leaf	Not specified	Guinea	Domis and Oyen (2008)
	Plant	Not specified	French Guyana	Schmelzer (2001)
	Not specified	Not specified	Jamaica	Mitchell and Ahmad (2006)
Filariasis	Not specified	Not specified	Brazil	Britto et al. (2007)
Diarrhea with blood	Leaf	Decoction	Mexico	Robinson and López (1999)
Stomachache	Leaf	Decoction	Mexico	Robinson and López (1999)
	Root	Not specified	Brazil	Brandão et al. (2008)
	Leaf	Infusion	Cuba	Pino et al. (2005)
	Leaf or root	Decoction	Africa	Domis and Oyen (2008)
	Leaf	Infusion	Nigeria	Ndukwu and Ben-Nwadibia (in press)
	Leaf	Not specified	Nigeria	Mensah et al. (2008)
	Leaf	Decoction	South-East Asia	Schmelzer (2001)
Colic	Leaf	Infusion	Liberia	Domis and Oyen (2008)
	Leaf and fruit	Not specified	Indochina	Schmelzer (2001)
Emollient	Leaf	Not specified	Africa	Domis and Oyen (2008)
Rectal prolapse	Leaf	Crushed, as an enema	Africa	Domis and Oyen (2008)
Piles	Flower, leaf	Decoction	Cameroon	Jiofack et al. (2008)
Nausea	Not specified	Not specified	Cameroon	Chartol (1964)
Scurvy	Seed (essential oil)	Oral	West Indies	Chenu (1986)
Burps	Leaf	Decoction	Dominican Republic	Roersch**
Skin				
Pimples and purulent pimples	Leaf	Decoction in poultice	Mexico	Zamora-Martínez and Pola (1992)
Skin irritation	Leaf	Poultice in water	Brazil	Hammer and Johns (1993)
	Leaf	Not specified	São Tomé and Príncipe	Martins et al. (1998)
External ulcers	Leaf	Decoction, infusion	Brazil	Grandi et al. (1989)
Abscesses	Leaf	Applied on the abscesses	South-East Asia	Schmelzer (2001)
	Leaf, root	Not specified	Dominican Republic	Liogier (2000)
	Leaf	Not specified	Haiti	Liogier (2000)
Boils	Leaf	Not specified	Brazil	Fenner et al. (2006)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
	Root	Not specified	Jamaica	Asprey and Thornton (1954)
	Not specified	Not specified	Jamaica	Mitchell and Ahmad (2006)
	Leaf	Poultice	Africa	Domis and Oyen (2008)
Burns	Root	Not specified	Brazil	Brandão et al. (2008)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
	Not specified	Sap	Dominican Republic	Liogier (2000)
	Not specified	Sap	Haiti	Liogier (2000)
	Leaf	Poultice	Africa	Domis and Oyen (2008)
Respiratory tract				
Catarrhs	Root	Syrup	Jamaica	Grieve (in press)
Cold	Root	Syrup	Jamaica	Grieve (in press)
	Whole plant	Tea	Jamaica	Asprey and Thornton (1954)
	Not specified	Not specified	Jamaica	Mitchell and Ahmad (2006)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
	Leaves with *Piper auritum*	Tea	Costa Rica	Hazlett (1986)
Bronchitis	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
Cough	Leaves with *Piper auritum*	Tea	Costa Rica	Hazlett (1986)
	Fruit with *Piper betle*	Chewed	Malaysia	Schmelzer (2001)
Breast infection	Flower, leaf	Decoction	Cameroon	Jiofack et al. (2008)
Angina	Not specified	Not specified	Cameroon	Chartol (1964)
Lung indications	Seed	Powder externally	West Indies	Chenu (1986)
Liver				
Liver	Root	Not specified	Brazil	Desmarchelier et al. (1997), Rodrigues and Guedes (2006)

Table 1 (*Continued*)

Medicinal use	Part used	Application*	Country	References
	Root	Decoction	Brazil	Kijjoa et al. (1980)
	Inflorescence	Decoction	Brazil	Agra et al. (2007)
	Not specified	Not specified	Brazil	Britto et al. (2007)
	Root	Decoction	Brazil	Mentz et al. (1997)
	Leaves with almond oil	Decoction, in lotion, externally	Brazil	Mentz et al. (1997)
	Leaf	Tea	Brazil	Coelho and Silva (in press)
	Leaf	Not specified	Brazil	Coelho et al. (2002), Vieira and Martins (2000)
	Leaf	Macerate in water	Brazil	Di Stasi et al. (2002)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
	Root	Not specified	Dominican Republic	Liogier (2000)
	Root	Not specified	Haiti	Liogier (2000)
Jaundice	Leaf or root	Decoction	Africa	Domis and Oyen (2008)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
Spleen	Root	Decoction	Brazil	Mentz et al. (1997), Rodrigues and Guedes (2006)
Bile	Leaf	Not specified	Africa	Domis and Oyen (2008)
Fever				
Sudorific	Root	Not specified	Brazil	Brandão et al. (2008)
Fever, Febrifuge	Leaf	Decoction	Brazil	Hammer and Johns (1993), Oliveira et al. (2003)
	Leaf	Eaten, fresh or dried	Brazil	Hammer and Johns (1993)
	Leaf	Body, rub	Brazil	Estrella (1995)
	Not specified	Not specified	Brazil	Britto et al. (2007)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
	Leaf	Pounded with water, as a bath	Gabon	Akendengue and Louis (1994)
	Not specified	Not specified	Gabon	Bodinga-bwa-Bodinga and Van der Veen (1993)
	Leaf	Decoction, as a wash	Africa	Domis and Oyen (2008), Schmelzer (2001)
Pains				
Body ache	Not specified	Infusion	Brazil	Stehmann and Brandâo (1995)
Muscular pain	Leaf	Infusion	Brazil	Di Stasi et al. (2002)
	Not specified	Not specified	Gabon	Bodinga-bwa-Bodinga and Van der Veen (1993)
Headache	Inflorescence	Decoction	Brazil	Agra et al. (2007)
	Leaf	External, warm	Dominican Republic	Roersch**
	Leaf	Not specified	Africa	Domis and Oyen (2008), Schmelzer (2001)
	Leaf	Tied on the head	Jamaica	Asprey and Thornton (1954)
	Not specified	Not specified	Jamaica	Mitchell and Ahmad (2006)
	Not specified	Not specified	Cameroon	Chartol (1964)
Migraine	Inflorescence	Decoction	Brazil	Agra et al. (2007)
	Leaf	Massage	Africa	Domis and Oyen (2008), Schmelzer (2001)
	Not specified	Not specified	Gabon	Bodinga-bwa-Bodinga and Van der Veen (1993)
Analgesic	Leaf	Warm, placed on the affected area	Venezuela	Díaz and Ortega (2006)
	Leaf	Not specified	Congo	Bioka and Abena (1990)
Toothache	Leaf	Maceration	Cameroon	Noumi et al. (1999), Noumi and Dibakto (2000)
Abdominal pains	Root	Infusion	São Tomé and Príncipe	Sequeira (1994)
Earache	Leaf	Juice, as drops	Africa	Domis and Oyen (2008)
Inflammation				
Anti-inflammatory	Root	Not specified	Brazil	Desmarchelier et al. (1997)
	Leaf	Wrapped around the irritated area	Mexico	Kashanipour and McGee (2004)
	Leaf	Not specified	Cuba	Pino et al. (2005)
Swelling and inflammation of the legs	Not specified	Not specified	Brazil	Britto et al. (2007)
Inflamed tumors	Root	Decoction in alcohol (dry gin)	Nigeria	Ndukwu and Ben-Nwadibia (in press)
	Leaf or root	Decoction	Africa	Domis and Oyen (2008)

Table 1 (*Continued*)

Medicinal use	Part used	Application*	Country	References
Wounds				
Wounds	Root	Not specified	Brazil	Brandão et al. (2008)
	Leaf	Decoction, in bath	Brazil	Rodrigues and Guedes (2006)
	Leaf	Not specified	São Tomé and Príncipe	Martins et al. (1998)
	Leaf or root	Decoction	Africa	Domis and Oyen (2008)
	Leaf	Fresh, applied on wounds	South-East Asia	Schmelzer (2001)
	Leaf	Decoction	Cameroon	Chartol (1964)
	Not specified	Not specified	Gabon	Bodinga-bwa-Bodinga and Van der Veen (1993)
Antiseptic	Leaf	Not specified	Africa	Domis and Oyen (2008)
Erysipelas	Not specified	Not specified	Brazil	Britto et al. (2007)
Swellings, contusions				
Contusions, bruises	Leaf	Fresh, applied on wounds	South-East Asia	Schmelzer (2001)
	Leaf	Warm, placed on the affected area	Brazil	Hammer and Johns (1993)
	Leaf	Poultice (with cow intestines)	Brazil	Estrella (1995)
Cuts and sprains	Leaf	Warm, placed on the affected area	Brazil	Hammer and Johns (1993)
Swellings	Leaf	Not specified	São Tomé and Príncipe	Martins et al. (1998)
	Leaf	Poultice	Africa	Domis and Oyen (2008)
	Leaf	Juice, rubbed on the affected part	Zimbabwe	Yamada (1999)
	Leaf	Warm, placed on the affected area	Brazil	Hammer and Johns (1993)
Dropsy	Leaf	Not specified	Nigeria	Ndukwu and Ben-Nwadibia (in press)
	Leaf and fruit	Not specified	Indochina	Schmelzer (2001)
Ascites	Leaf	Infusion	Nigeria	Ndukwu and Ben-Nwadibia (in press)
Rheumatism				
Rubefacient	Fruit	Not specified	Nigeria	Ndukwu and Ben-Nwadibia (in press)
Rheumatic pains	Fruit	Not specified	Nigeria	Ndukwu and Ben-Nwadibia (in press)
Rheumatism	Root	Decoction in alcohol (dry gin)	Nigeria	Ndukwu and Ben-Nwadibia (in press)
	Leaf	Friction	Ghana	Domis and Oyen, 2008
	Seed	Powder, externally	West Indies	Chenu, 1986
Sundries				
Tonic	Leaf, stem	Stems and leaves ashes on scarification	Burundi	Polygenis-Bigendako (1990)
Kwashiorkor	Leaf, stem	Stems and leaves ashes on scarification	Burundi	Polygenis-Bigendako (1990)
Syphilis	Leaf or root	Decoction	Africa	Domis and Oyen (2008)
	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
Gonorrhea	Leaf or root	Decoction	Africa	Domis and Oyen (2008)
Depurative	Leaf, root	Decoction, infusion	Brazil	Grandi et al. (1989)
Conjunctivitis	Leaf	Juice	Philippines	Schmelzer (2001)
Anemia	Leaf and fruit	Not specified	Indochina	Schmelzer (2001)
Against poisons	Root	Not specified	Jamaica	Grieve (in press)
Hypertension	Leaf	Maceration	Cameroon	Noumi et al. (1999)
	Leaf	Decoction	Comoros Islands	Kaou et al. (2008)
Diabetes	Leaf	Decoction	Comoros Islands	Kaou et al. (2008)
Malaria	Leaf	Nasal drops	Guinea Equatorial	Akendengue (1992)
	Leaf or root	Decoction	Africa	Domis and Oyen (2008)
	Leaf and root	Not specified	Brazil	Oliveira et al. (2003)
Epilepsy	Root	Decoction	Brazil	Kijjoa et al. (1980)
	Root	Not specified	Brazil	Britto et al. (2007)
Aphrodisiac	Root	Decoction	East Africa	Kokwaro (1976), in Hammer and Johns (1993)
Infertility	Root	Not specified	Congo	Nkounkou-Loumpangou et al. (2005)
Sedative	Not specified	Not specified	Congo	Bioka and Abena (1990)
Tiredness (Asthenia)	Root	Not specified	Brazil	Brandão et al. (2008)
Immunostimulant	Root	Not specified	Brazil	Brandão et al. (2008)

* If not specified, decoction, infusion, juice and maceration are used orally.
** Data from our National Study.

Table 2
Chemical constituents of *Piper umbellatum*.

Component	Plant part	References
Alkaloids		
N-Benzoylmescaline	Aerial parts	Isobe et al. (2002)
N-Hydroxyaristolam II	Branches	Tabopda et al. (2008)
Piperumbellactams (A–D)	Branches	Tabopda et al. (2008)
Potomorphine	Leaves	Hegnauer (1969)
Flavonoids		
Acacetin 6-C-β-D-glucopyranoside	Branches	Tabopda et al. (2008)
Acacetin 3-O-β-D-[6′-dodecanoyl]-glucopyranoside	Branches	Tabopda et al. (2008)
Acacetin 3-O-β-D-glucopyranoside	Branches	Tabopda et al. (2008)
Apigenin 8-C-neohesperidoside	Branches	Tabopda et al. (2008)
Uvangoletin	Aerial parts	Isobe et al. (2002)
Wogonin	Aerial parts	Isobe et al. (2002)
Sterols		
Campesterol	Aerial parts	Sacoman et al. (2008)
β-Sitosterol	Aerial parts	Isobe et al. (2002), Sacoman et al. (2008), Tabopda et al. (2008)
β-Sitosterol	Leaves, roots	Kijjoa et al. (1980)
Stigmasterol	Aerial parts	Sacoman et al. (2008)
Terpenes		
β-Amyrin	Branches	Tabopda et al. (2008)
Bicyclogermacrene	Essential oil*, leaves	Luz et al. (1999), Mesquita et al. (2005), Pino et al. (2005)
Cadinene	Essential oil, leaves	Chartol (1964)
δ-Cadinene	Essential oil, leaves	Luz et al. (1999), Mesquita et al. (2005), Pino et al. (2005)
β-Caryophyllene	Essential oil, leaves	Luz et al. (1999), Maia and Andrade (2009), Martins et al. (1998), Mesquita et al. (2005), Pino et al. (2005), Vogler et al. (2006), Chartol (1964)
Caryophyllene oxide	Essential oil, leaves	Luz et al. (1999), Mesquita et al. (2005)
α-Copaene	Essential oil, leaves	Luz et al. (1999)
α-Cubebene	Essential oil, leaves	Luz et al. (1999)
Cubebol	Essential oil, leaves	Luz et al. (1999)
10-epi-gamma-Eudesmol	Essential oil, leaves	Mesquita et al. (2005)
Epizonarene	Essential oil, leaves	Luz et al. (1999)
(*E*,*E*)-α-Farnesene	Essential oil, leaves	Vogler et al. (2006)
Friedelin	Branches	Tabopda et al. (2008)
α-Humulene	Essential oil, leaves	Luz et al. (1999)
Germacrene D	Essential oil, leaves	Luz et al. (1999), Maia and Andrade (2009), Mesquita et al. (2005), Pino et al. (2005), Vogler et al. (2006)
Limonene	Essential oil, leaves	Martins et al. (1998)
Linalool	Essential oil, leaves	Martins et al. (1998)
(*E*)-Nerolidol	Essential oil, leaves	Maia and Andrade (2009), Martins et al. (1998), Mesquita et al. (2005), Pino et al. (2005)
(*E*)-β-Ocimene	Essential oil, leaves	Martins et al. (1998)
(*Z*)-β-Ocimene	Essential oil, leaves	Martins et al. (1998)
Phellandrene	Essential oil, leaves	Chartol (1964)
Phytol	Essential oil, leaves	Martins et al. (1998)
α-Pinene	Essential oil, leaves	Martins et al. (1998)
β-Pinene	Essential oil, leaves	Martins et al. (1998)
Spathulenol	Essential oil, leaves	Luz et al. (1999), Mesquita et al. (2005), Pino et al. (2005)
Trans-Dihydroagarofurane	Essential oil, leaves	Mesquita et al. (2005)
β-Elemene	Essential oil, leaves	Mesquita et al. (2005)
β-Gurjunene	Essential oil, leaves	Luz et al. (1999)
α-Acorenol	Essential oil, leaves	Luz et al. (1999)
Others		
4-Nerolidylcatechol	Roots, whole plant, leaves	Bergamo et al. (2005), De Oliveira and Akisue (1984), Desmarchelier et al. (1997), Kijjoa et al. (1980), Núñez et al. (2005), Tabopda et al. (2008), Viana et al. (2000)
Dillapiol	Leaves	Bernhard and Thiele (1978)
E-3-(3,4-dihydroxyphenyl)-*N*-2-[4-hydroxyphenyletyl]-2-propenamide	Branches	Tabopda et al. (2008)
Heneicosane	Essential oil, leaves	Maia and Andrade (2009)
N-*p*-Coumaroyl tyramine	Branches	Tabopda et al. (2008)
N-*trans*-Feruloyl tyramine	Branches	Tabopda et al. (2008)
Safrole	Essential oil, leaves	Pino et al. (2005)
Cinnamic acid	Leaves	Chartol (1964)
2-(4′,8′-dimethylnona-3′7′-dienyl)-8-hydroxy-2-methyl-2H-chromene-6-carboxylic methyl ester	Branches	Núñez et al. (2005)

* Only the main components of the essential oil are mentioned (>1.0%).

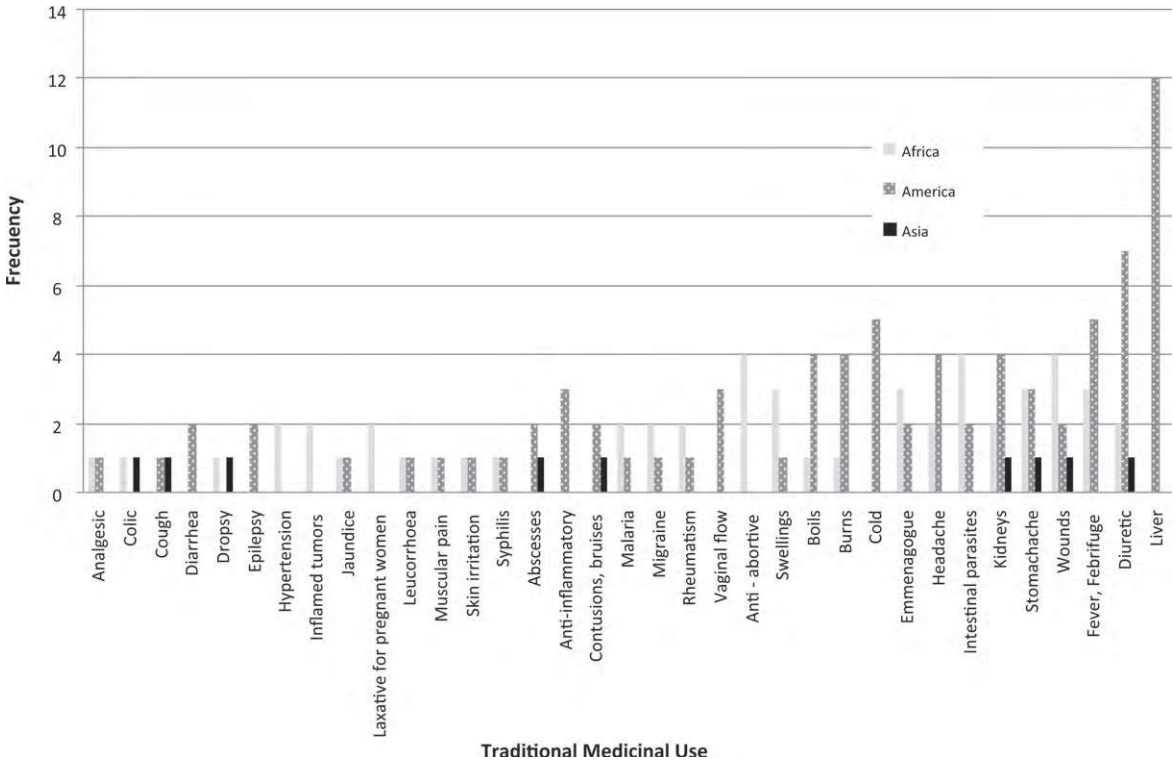

Fig. 1. Traditional medicinal uses in two or more countries in one or more continents. References see Table 1.

the chemical identification or the use of fingerprints in the extracts must be taken into account.

5. Pharmacology

The extracts and pure compounds derived from *P. umbellatum* show a wide spectrum of pharmacological activities, including antibacterial, anti-inflammatory, analgesic, antioxidant, cytotoxic, antimalarial, antileishmanial, antitrypanosomal and other activities (Table 4). Pharmacological activities in *in vitro* and *in vivo* experiments are taken as starting points for the development of clinical studies. The concentrations by which these activities occur, whether expressed in IC_{50}, MIC, ED_{50}, etc., are crucial. Lately, efforts have been undertaken to obtain a more coherent, standardized approach. Adequate concentrations for anti-infective bioassays should be less than 100 μg/ml for extracts and mixtures and below 25 μM for compounds (Cos et al., 2006). Gertsch (2009) goes even further and proposes 50 μg/ml for extracts and 5 μM for compounds. For *in vivo* experiments, Gertsch (2009) questions if doses of 200 mg/ml or more are of any practical use. Inclusion of controls in bioassays is very important and determines the effective dose order of the extract or isolated compound. In the following assessment of the various pharmacological activities of *P. umbellatum*, these criteria will be applied.

5.1. Antifungal activity:

In the case of the Dominican Republic, it is very interesting to know whether antifungal activity is demonstrated for *P. umbellatum*. In our study, the main traditional use is vaginal flow (locally called 'flujo blanco' or 'flor blanca'), which is frequently caused by a *Candida albicans* infection. Tabopda et al. (2008) tested three secondary metabolites, Piperumbellactam D, *N*-hydroxyaristolam II and 4-nerolidylcatechol, which showed high activity against a

Table 3
Comparison of the essential oils of *P. umbellatum* in different countries.

Component (% in samples)	Country					
	Brazil (Maia and Andrade, 2009)*	Brazil (Luz et al., 1999)	Brazil (Mesquita et al., 2005)	Costa Rica (Vogler et al., 2006)*	Cuba (Pino et al., 2005)	São Tomé and Príncipe (Martins et al., 1998)
β-Caryophellene	37.5	14.8	12.6/10.2	28	4.6	9.8
Germacrene D	11.9	27.4	8.6/27.4	17	7.9	–
Heneicosane	1.2	–	–	–	–	–
(*E*)-Nerolydol	9.1	0.7	7.0/7.9	–	1.1	12.4
β-Pinene	–	–	0.1	–	0.2	17.6
α-Pinene	–	–	Trace	–	0.1	26.8
Bicyclogermacrene	–	11.5	10.1/8.8	–	3.7	–
δ-Cadinene	–	13.3	–	–	5.6	0.1
(*E*,*E*)-α-Farnesene	–	–	–	15	–	0.7
β-Elemene	–	–	6.7/6.4	–	–	–
Trans-dihydroagarofurane	–	–	6.6/–	–	–	–
Safrole	–	–	–	–	48.7	–

* Only the main constituents were mentioned.

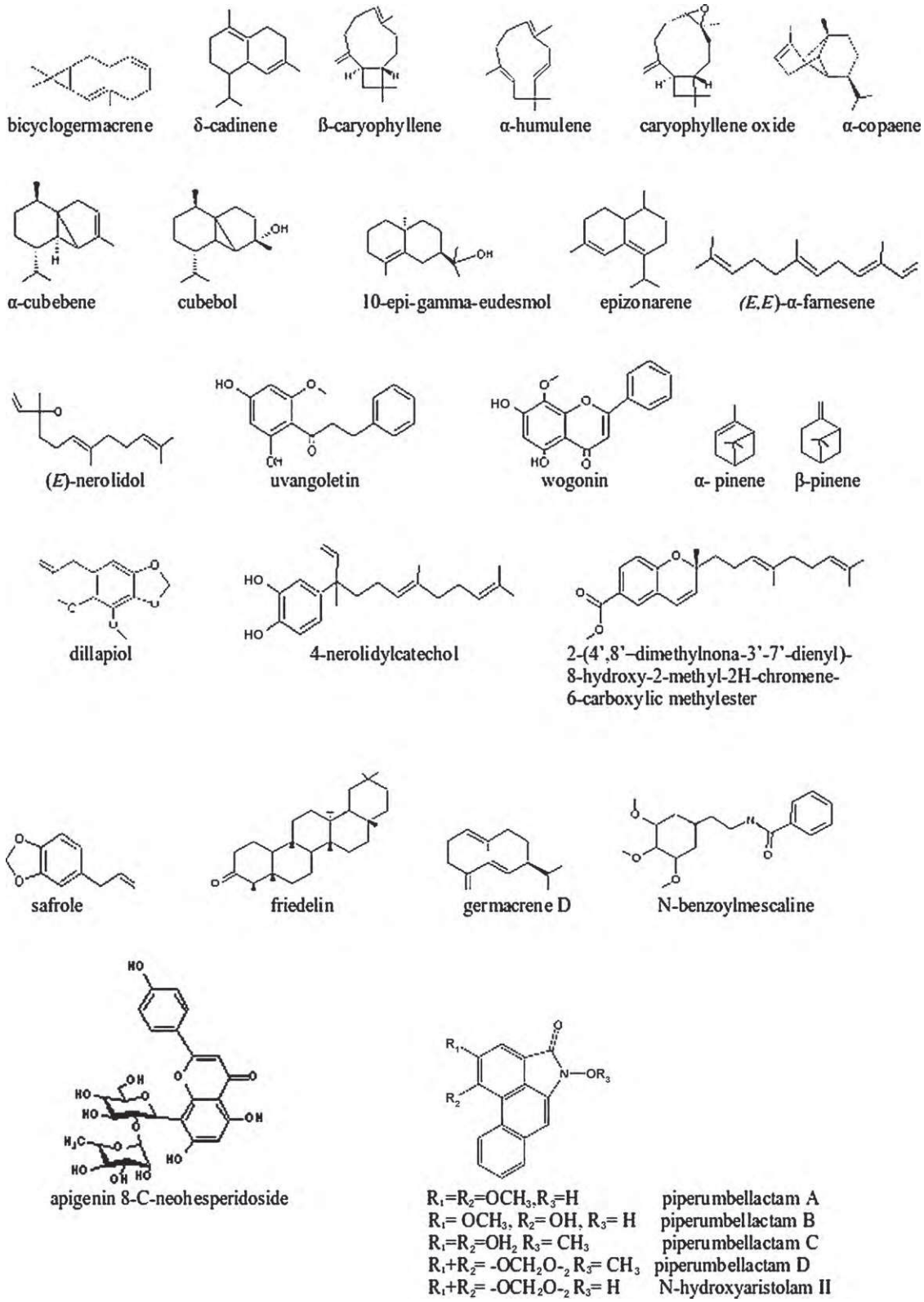

Fig. 2. Structures of some chemical constituents of *P. umbellatum*.

series of fungi, including *C. albicans*. The first two demonstrated an even higher activity against *S. flavus* and *T. longifusus* than did amphotericin B. The authors suggested that the presence of the methylenic carbon in methylenedioxyphenyl (MDP) is more able to form a stable carbene under oxidation. However, further research is needed in *in vivo* and in clinical studies to confirm these initial findings. A classification system that was apparently proposed by Aligiannis et al. (2001) is used in the literature and is based on MIC values (for extracts), as follows: strong inhibitors – MIC up to 0.5 mg/ml; moderate inhibitors – MIC between 0.6 and 1.5 mg/ml; weak inhibitors – MIC above 1.6 mg/ml. However, the indicated reference proposes anything but a classification. These concentra-

tions are much higher than those suggested by Cos et al. (2006) and Gertsch (2009).

5.2. Antioxidant activity and skin protection

The extracts of various parts of *P. umbellatum* and several isolated compounds show interesting antioxidant activities. It is known that one of the traditional medicinal uses with consensus is in the treatment of wounds, and antioxidants play a well-known role in wound healing (Sen et al., 2002; Soneja et al., 2005). Thus, we have indirectly confirmed our hypothesis. We recommend that further research be pursued in this area. Some problems need to be taken into account, however. It is observed that the extract shows a higher value compared to 4NC, which could imply the presence of other antioxidant compounds in the extract (Desmarchelier et al., 1997). The free and total antioxidant capacity of several *Piper* sp. (methanolic leaf extract) were studied, using two different methods, the Folin–Ciocalteu reagent (Folin) and the ferric reducing antioxidant power (FRAP). There was no significant correlation between the Folin and FRAP free oxidant capacity, though there was a highly significant correlation between the Folin and FRAP total antioxidant capacity. It was concluded that the results of antioxidant activity using different methods should be interpreted carefully (Agbor et al., 2005). In Brazil, this antioxidant activity was the starting point for studying the effect of the root extract of *P. umbellatum* on skin damage produced by UV radiation. Prolonged UV exposure can cause severe depletion of skin antioxidants (like α-tocopherol), which could lead to skin cancer and photoaging. The depletion of α-tocopherol was avoided by applying a gel with the ethanolic extract of the roots of *P. umbellatum* on the skin of hairless mice exposed to UV-B radiation (Ropke et al., 2003). Also, after chronic exposure to UV-B radiation, these hairless mice were clearly protected from skin wrinkling. This means that the plant can be used as a photoprotective agent (Ropke et al., 2005). Investigating the possible underlying mechanism of the prevention of photoaging by *P. umbellatum*, Ropke et al. (2006) looked at the relationship between the root extract of *P. umbellatum* and matrix metalloproteinases (MMP), specifically MMP-2 and MMP-9. The ethanolic extract was able to inhibit MMP-9 activity *in vitro* as well as *in vivo*. The effect of the extract was stronger than that of 4NC (Ropke et al., 2006). The synthesis of these MMP is upregulated by the exposure of human skin to UV radiation. Possible application of the gel of the ethanolic extract of the roots can endanger the existence of the species. Therefore, Almeida et al. (2008) investigated the photostability of the ethanolic extract of the leaves of *P. umbellatum*, which contain 30% less 4NC. The outcome was that the extract is stable under UV-B radiation and inhibits the MMP-2 and MMP-9 activity of hairless mice *in vitro*. In the USA and other countries, Barros and Ropke have patented the effects of *P. umbellatum* on the skin (Anonymous, 2004). Optimization of the emulsion concerning the appearance, centrifuge stability and permeation has already been performed (Noriega et al., 2008).

5.3. Antimalarial activity

Several studies have been performed on the antiplasmodial activity of *P. umbellatum*. The ethanolic extract of the leaves, applied orally as well as subcutaneously in mice, has antimalarial activity against *Plasmodium berghei* (Amorim et al., 1988). However, Ferreira-da-Cruz et al. (2000) found that mice infected intraperitoneally with *P. berghei* Pasteur is not a good test system to detect the antiplasmodial activity. They discovered a 'slow' and 'fast' pattern of parasitemia. Some of the infected animals have a normal (fast) pattern, in which parasitemia increases quickly from the day of infection, and part of the animals have a low pattern, in which the parasitemia only starts to increase at day four of the infection (normally the day when antimalarial activity is evaluated). Intravenously infected animals did not show this effect. The presented studies show that it is important to consider the particular strain of *Plasmodium falciparum*. Andrade-Neto et al. (2007) and Kamanzi Atindehou et al. (2004) have positive results at very interesting concentrations using strain K1. On the contrary, Kaou et al. (2008) consider the dichloromethane, methanol and methanol/water (1/1) extracts (aerial parts) as having no activity against the chloroquine-resistant strain W2 of *P. falciparum*. A comparable finding is given by Bidla et al. (2004) concerning the chloroquine-sensitive F32 strain. Unfortunately, the promising result of the active principle, 4-nerolidylcatechol, concerning the chloroquine, pyrimethamine and cycloguanil resistant *P. falciparum* strain K1 (Andrade-Neto et al., 2007), has not been evaluated so far *in vivo*.

5.4. Other biological activities

There are several biological activities investigated for *P. umbellatum*, which show positive effects at interesting concentrations. These studies demonstrated potential cytotoxic and anti-tumoral activity (Anonymous, 1976; Brohem et al., 2009; Kamanzi Atindehou et al., 2004; Sacoman et al., 2008; Werka et al., 2007), antibacterial activity (Isobe et al., 2002), antileishmanial activity (Braga et al., 2007) and antitrypanosomal activity (Kamanzi Atindehou et al., 2004). These studies are still at an initial stage and need to be reproduced and confirmed. No follow-up research has been reported so far.

5.5. Pharmacological activities versus traditional medicinal uses

In traditional medical systems *P. umbellatum* covers a wide range of medicinal uses (Table 1). Comparing these uses with the existing pharmacological literature (Table 4) shows us that the majority of the traditional uses lack a pharmacological basis. Some traditional uses are being investigated, like malaria, which caught the interest of several authors (see Section 5.3), and vaginal flow (see Section 5.1). Analgesic and anti-inflammatory activity has been shown for the water and water–ethanolic extract of *P. umbellatum*. However, these effects are registered at relatively high concentrations. The traditional uses with consensus for *P. umbellatum* are kidney, diuretic, stomachache and wounds. Also, skin affections are mentioned in many countries. Up to now, pharmacological experiments directly dealing with these traditional uses have not been performed. The proposed hypothesis – the same (consensus) uses of a plant in different cultures should have a scientific basis – has not been confirmed. However, in the case of wounds (see Section 5.3), there is indirect proof for this hypothesis. It would be challenging to see if these claimed traditional uses with consensus indeed have a pharmacological justification. One can argue that the world is not waiting for a new diuretic, but validating this broadly diffused medicinal use will be important for the incorporation of *P. umbellatum* as a diuretic in Primary Health Care in many countries.

6. Toxicology

Applied orally to mice, the ethanolic extract (70%, conc.: 500–2000 mg/kg) of the aerial parts did not produce any deaths during the 72-h period in the acute toxicity test, which means a LD_{50} higher than 2.0 g/kg (Perazzo et al., 2005). However, the dichloromethane extract of the aerial parts, given intraperitoneally, resulted in a LD_{50} of 533.71 mg/kg. The highest applied dose of 1000 mg/kg produced death (Sacoman et al., 2008). A water suspension of the dried root ethanolic extract was given, via catheter, to rats in a concentration of 1, 2 and 5 g/kg. For 14 days the rats were observed. No deaths or signs of intoxication were registered. Subchronic toxicity was determined by giving the rats, via

Table 4
Biological and pharmacological activities (*in vitro* and *in vivo*) of *P. umbellatum* extracts and pure compounds.

Extract/compound	Biological and pharmacological activity	References
ANTIBACTERIAL ACTIVITY		
N-Benzoylmescaline (conc. 2.5 μg/ml)	*In vitro* antibacterial activity against *Helicobacter pylori*	Isobe et al. (2002)
Essential oil (leaf, conc. 100 μg/ml)	Inhibition of the growth of *Bacillus cereus* (MIC = 1250 μg/ml) and *Staphylococcus aureus* (MIC = 156 μg/ml)	Werka et al. (2007)
ANTIFUNGAL ACTIVITY:		
Methanol extract of the leaves (conc. 100 mg/ml)	*In vitro* inhibitory activity against *Candida albicans* (MIC = 2.50 mg/ml) and *C. neoformans* (MIC = 625 μg/ml) using the agar-well diffusion assay with amphotericin B as positive control	Braga et al. (2007)
Piperumbellactam D (conc. 200 μg/ml or 0.68 μM)	Inhibition of radial growth of *Trichophyton longifusus* (73%), *Candida albicans* (101%), *Aspergillus favus* (35%), *Microsporum canis* (90%), *Fusarium solani* (63%) and *Candida glabrata* (101%) using the agar tube dilution method (with miconazole and amphotericin B as controls)	Tabopda et al. (2008)
N-hydroxyaristolam II (conc. 200 μg/ml or 0.71 μM)	Inhibition of radial growth of *Trichophyton longifusus* (89%), *Candida albicans* (108%), *Aspergillus favus* (51%), *Microsporum canis* (87%), *Fusarium solani* (65%) and *Candida glabrata* (99%) using the agar tube dilution method (with miconazole and amphotericin B as controls)	Tabopda et al. (2008)
4-Nerolidylcatechol (4NC) (conc. 200 μg/ml or 0.64 μM)	Inhibition of radial growth of *Trichophyton longifusus* (50%), *Candida albicans* (55%), *Aspergillus favus* (10%), *Microsporum canis* (50%), *Fusarium solani* (49%) and *Candida glabrata* (78%) using the agar tube dilution method (with miconazole and amphotericin B as controls)	Tabopda et al. (2008)
ANTIOXIDANT ACTIVITY		
Methanolic extract of the roots 4-Nerolidylcatechol (4NC)	*In vitro* antioxidant activity measured as total reactive antioxidant potential (TRAP) and the total antioxidant reactivity (TAR) using the luminol-enhanced chemiluminescence by peroxyl radicals method and catechin as a standard (extract/4NC/catechin: TRAP 97.2 ± 10.8 μM/33.6 ± 23.0 μM/20.4 ± 9.0 μM; TAR 0.6 ± 0.1 μM/4.9 ± 0.2 μM/3.1 ± 1.0. IC_{50} values were: 13.3 μg/ml (extract) and 4.9 μg/ml (4NC)) *In vitro* inhibition of free radical-mediated DNA-sugar damage induced by the presence of Fe(II) salts (extract/4NC: IC_{50}: 21 and 8 μg/ml)	Desmarchelier et al. (1997)
Ethanolic extracts of the root, stem and leaves	*In vitro* antioxidant activity in brain tissue auto-oxidation evaluated by using malondialdehyde (MDA) and chemiluminescence (CL). $Q_{1/2}$ of the ethanolic extracts of the roots, stems and leaves were 4.0, 19.3 and 38.5 μg/ml, respectively	Barros et al. (1996)
Methanolic extract and methanolic extract with HCl of the leaves	*In vitro* antioxidant activity in the Folin–Ciocalteu reagent (Folin) and the ferric reducing antioxidant power (FRAP) method	Agbor et al. (2005)
Methanolic extract of the leaves	*In vitro* scavenging effect on DPPH (1,1-diphenyl-2-picrylhydrazyl) (79.8–89.9% at a dose level of 10 mg/ml), nitric oxide (85.1–97.9%, dose level 10 mg/ml), the superoxide radical (47.1–51.6%, dose level 8 mg/ml) and the hydroxyl radical (57–76.1%, dose level 5 mg/ml) and a 0.4–0.6 reducing power and a 88.3–93.9% metal chelating activity at a dose level of 8 mg/ml	Agbor et al. (2007)
Piperumbellactam A Piperumbellactam B Piperumbellactam C *N*-*p*-Coumaroyl tyramine (conc. 10 μM)	*In vitro* inhibitory activity in the DPPH radical scavenging assay with caffeic acid as positive control (13.1%, 67.8%, 86.4% and 61.8%, respectively, at a conc. of 10 μM)	Tabopda et al. (2008)
CYTOTOXIC ACTIVITY		
Water–ethanol extract of the stem	*In vitro* cytotoxic activity against CA-9KB	Anonymous (1976)
Dichloromethane extract of the aerial parts	*In vitro* antiproliferative activity against the human cancer cell lines MCF-7, NCI-ADR/RES, OVCAR-3, PC-3, HT-29, NCI-H460, 786-O, UACC-62, K-56 (total growth inhibition, TGI, between 4.0 and 9.5 μg/ml) and the leukemia cell line K-652 (TGI = 1.55 μg/ml)	Sacoman et al. (2008)
Dichloromethane extract of the aerial parts (conc. 100, 200, 300, and 400 mg/ml)	*In vivo* anti-tumor activity by intraperitoneal administration, evaluated with the Ehrlich ascites tumor model in mice	Sacoman et al. (2008)
4-Nerolidylcatechol	*In vitro* cytotoxic activity against melanoma cell lines SK-Mel-28, SK-Mel-103 and SK-Mel-147 (IC_{50} = 20–40 μM)	Brohem et al. (2009)
Ethanolic extract of the stem and leaf	*In vitro* cytotoxic activity against L-6 rat skeletal myoblast cells (IC_{50} = 61.3 μg/ml)	Kamanzi Atindehou et al. (2004)
Essential oil (leaf, conc. 100 μg/ml)	*In vitro* cytotoxic activity against Hep G2 (hepatocellular carcinoma) (10% kill); no activity (0% kill) found against MCF-7 and PC-3 human tumor cells	Werka et al. (2007)
ANTIMALARIAL ACTIVITY		
Ethanolic extract of the stem and leaf	*In vitro* antiplasmodial activity against *Plasmodium falciparum* (strain K1, resistant to chloroquine and pyrimethamine) (IC_{50} = 3.74 μg/ml)	Kamanzi Atindehou et al. (2004)
Dichloromethane extract of aerial parts Methanol extract of aerial parts Methanol/water (1/1) extracts of aerial parts	*In vitro* antimalarial activity against the chloroquine-resistant strain W2 of *Plasmodium falciparum* (IC_{50} = >50, >50 and 50 μg/ml, respectively)	Kaou et al. (2008)
4-Nerolidylcatechol	*In vitro* activity against the chloroquine, pyrimethamine and cycloguanil resistant *P. falciparum* strain K1 (IC_{50} = 0.67 nM)	Andrade-Neto et al. (2007)
Chloroform/methanol extract (1/1) of the leaves	*In vitro* inhibition of chloroquine-sensitive F32 strain of *P. falciparum* (70% inhibition at 40 μg/ml)	Bidla et al. (2004)

Table 4 (*Continued*)

Extract/compound	Biological and pharmacological activity	References
Ethanolic extract of the leaves	*In vivo* dose-dependent reduction in parasitemia (orally as well as subcutaneously) in mice (conc. orally 250 and 1250 mg/ml; subcutaneously 100 and 500 mg/ml)	Amorim et al. (1988)
ANALGESIC ACTIVITY		
Water extract of the leaves	*In vivo* analgesic effect in rats by intraperitoneal administration (no concentrations given, abstract only)	Bioka and Abena (1990)
Water–ethanolic extract of the leaves	Significant *in vivo* analgesic activity in rats by granulomatous tissue induction and the writhing test by a daily oral administration of 550 mg/kg extract	Perazzo et al. (2005)
ANTIINFLAMMATORY ACTIVITY		
Water–ethanolic extract of the aerial parts	Significant *in vivo* anti-inflammatory activity by using carrageenan-induced rat paw edema (ED_{50} = 550 mg/kg, orally)	Perazzo et al. (2005)
OTHER PHARMACOLOGICAL ACTIVITIES		
4-Nerolidylcatechol	*In vitro* inhibition of myotoxin I, a phospholipase A2 of *Bothrops asper* (IC_{50} = 987 μM)	Núñez et al. (2005)
4-Nerolidylcatechol	Significant *in vivo* reduction of myotoxic and edema-inducing activities produced by *Bothrops* myotoxins in mice (preincubation with 100 or 200 μg 4NC)	Núñez et al. (2005)
Water extract of the leaves	Anti-crustacean activity (*Artemia salina*) (LD_{50} = 122.5 mg/ml)	Hammer and Johns (1993)
Essential oil of the leaves	Anti-crustacean activity (*Artemia salina*) (LD_{50} = 29.1 μg/ml)	Werka et al. (2007)
Water extract of the leaves	No significant inhibition *in vitro* of α- and β-glycosidase (no conc. given)	Hammer and Johns (1993)
Piperumbellactam A Piperumbellactam B Piperumbellactam C	*In vitro* activity against α-glycosidase (IC_{50} = 98.07, 43.80 and 29.64 μM, respectively)	Tabopda et al. (2008)
Ethanolic extract of the root	*In vitro* dose-related reduction of MMP-2, pro-MMP-2 and MMP-9 in the cornea of the rabbit (dose 50, 100, 250 μg/ml) (matrix metalloproteinases, MMP, are related to the failure of the cornea to re-epithelialize after injury)	Barros et al. (2007)
Ethanolic extract of the root in gel containing 0.1% 4-nerolidylcatechol	*In vivo* prevention (100%) of α-tocopherol depletion in the skin of hairless mice treated with *P. umbellatum* root extract gel after UV-irradiation	Ropke et al. (2003)
Ethanolic extract of the root in gel containing 0.1% 4-nerolidylcatechol	*In vivo* photoprotective effect of *P. umbellatum* root extract gel against UV irradiation-induced chronic skin damage (skin wrinkling) in hairless mice	Ropke et al. (2005)
Ethanolic extract of the root Ethanolic extract of the root in gel containing 0.1% 4-nerolidylcatechol	Strong *in vitro* inhibitory effect of *P. umbellatum* extract (100 μg/ml extract containing 7.09 μg/ml 4NC) on MMP-2 and MMP-9 measured by gelatin zymography *In vivo* inhibition of constitutive MMP-9 activity in mice sacrificed 2 h after UVB irradiation as measured by gelatin zymography and histological analysis	Ropke et al. (2006)
Methanolic extract of the leaves	*In vitro* antileishmanial activity against *Leishmania amazonensis* and *Leishmania chagasi* with amphotericin B as control drug (IC_{50} = 39 μg/ml and IC_{50} = >250 μg/ml, respectively)	Braga et al. (2007)
Ethanolic extract of the stem and leaf	In vitro antitrypanosomal activity against *Trypanosoma brucei rhodesiense* (IC_{50} = 2 μg/ml)	Kamanzi Atindehou et al. (2004)
Water extract of the leaves	Hypothermic and tranquilizing activity; ataxia and reduction of the spontaneous activity in rats by intraperitoneal administration (no concentration given; abstract only)	Bioka and Abena (1990)

catheter, a water suspension of the dried root ethanolic extract (conc. 500 mg/kg) for 40 days (5 days a week). No signs of intoxication or deaths were registered. The hematological parameters (conc. hemoglobin, erythrocytes, leukocytes) showed no alteration; concerning the serum biochemical parameters, the triglycerides increased 39% in male rats and the AST activity decreased 24% in female rats; serum proteins decreased in both sexes. There were no alterations in the liver, spleen, kidneys and heart; also, no mutagenic activity was detected in the bone marrow micronucleus test (Barros et al., 2005). Lajide et al. (1998) investigated the toxicity of *P. umbellatum* to the maize weevil (*Sitophilus zeamais* Mots.). Maize grains were treated with the plant powder at the rate of 0, 1, 5 and 10% by weight of maize grains and then infested with 10 adult weevils. *P. umbellatum*, at the 1% treatment level, gave 100% kill at 28 days of treatment. Chartol (1964) also described an effective action of *P. umbellatum* as an insecticide, but of the essential oil from the leaves.

Andrade et al. (2005) evaluated the mutagenic potential of the water–ethanolic extract (70%) of the aerial parts. The extract was given orally to Wistar rats at concentrations of 500, 1000 and 1500 mg/kg. This did not induce an increase in the average number of DNA damage in the liver cells and in the micronucleus in the bone marrow cells. There was, however, a significant increase in DNA damage in peripheral blood cells. In the *Salmonella*/mammalian-microsome assay, no mutagenic effect of the ethanolic extract (plant parts not specified; conc. 50, 100, 250, and 500 μg) was observed (Felzenszwalb et al., 1987). The ethanolic extract of the roots of *P. umbellatum* (dosis 50, 100 and 200 mg/kg/day, orally) did not demonstrate a mutagenic effect in mice using the micronucleus test. On the contrary, there was a protective effect against genotoxicity induced by cyclophosphamide. The effect of the isolated 4-nerolidylcatechol (dosis 12.5, 25 and 50 mg/kg/day, orally) was even better (Valadares et al., 2007).

From the above, one may conclude that the different extracts of *P. umbellatum* are not toxic and do not possess mutagenic effects, and even better, show protective qualities. Nevertheless, in the southwest of the Ivory Coast, in South-East Asia and in South America, *Piper umbellatum* is applied as a component of an arrow poison to hunt monkeys and wild pigs. In Colombia, the scraped, boiled bark of the lower part of the stem and root is used for this purpose (Domis and Oyen, 2008; Schmelzer, 2001; Schultes, 1980 in Hammer and Johns, 1993; Schultes and Raffauf, 1990). This finding

and the fact that the pulverized plant and the essential oil of the leaf have insecticidal activity make it necessary to do more research on the toxicity of *P. umbellatum*.

7. Conclusions

P. umbellatum is a widely appreciated medicinal plant and has cross–cultural uses in three continents. Traditional uses, on which major consensus exists, are kidney/diuretic, wounds and stomachache. Indirectly, the traditional use for wounds is supported. This interesting fact is the result of the demonstrated antioxidant effect of the plant and the role antioxidants play in wound healing. In Brazil, the antioxidant activity has been the starting point in the study of the effect of the root extract of *P. umbellatum* on skin damage produced by UV radiation. The outcome of this study is the formulation of a skin-protecting agent against UV radiation. These findings have been patented and the development of a cosmetic product is in progress. Critical assessment of the biological and pharmacological activities has shown that *P. umbellatum* may have interesting clinical applications, but there is still a tremendous distance between the existing pharmacological knowledge and any clinical application. Most experiments are at an initial, *in vitro* stage. There is an enormous shortage of *in vivo* studies, not to mention clinical studies. Moreover, the existing pharmacological data show differences in the activity of the extracts and the supposedly active compound, 4-nerolidylcatechol. The recently discovered bioactive constituents, piperumbellactams, indicate that much work still has to be done on the phytochemistry of the species. The presented differences in the contents of the essential oils of *P. umbellatum* make it very clear that for further comparison of experimental data, the chemical identification or the use of fingerprints in the extracts must be taken into account. The incongruent information about the toxicity of the species urges more research. This review indicates that *P. umbellatum* has a potential as a therapeutic agent, but the road to any clinical application is still very long.

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References

Agbor, G.A., Oben, J.E., Ngogang, J.Y., Xinxing, C., Vinson, J.A., 2005. Antioxidant capacity of some herbs/spices from Cameroon: a comparative study of two methods. Journal of Agricultural Food Chemistry 53, 6819–6824.

Agbor, G.A., Vinson, J.A., Oben, J.E., Ngogang, J.Y., 2007. *In vitro* antioxidant activity of three *Piper* species. Journal of Herbal Pharmacotherapy 7, 49–64.

Agra, M.deF., Freitas, P.F., Barbosa-Filho, J.M., 2007. Synopsis of the plants known as medicinal and poisonous in Northeast of Brazil. Brazilian Journal of Pharmacognosy 17, 114–140.

Akendengue, B., 1992. Medicinal plants used by the Fang traditional healers in Equatorial Guinea. Journal of Ethnopharmacology 37, 165–173.

Akendengue, B., Louis, A.M., 1994. Medicinal plants used by the Masango people in Gabon. Journal of Ethnopharmacology 41, 193–200.

Aligiannis, N., Kalpoutzakis, E., Mitaku, S., Chinou, I.B., 2001. Composition and antimicrobial activity of the essential oils of two *Origanum* species. Journal of Agriculture and Food Chemistry 49, 4168–4170.

Almeida, R.L., Silva, V.V., Rivelli, D.P., Miranda, D.V., Sawada, T.C.H., Barros, S.B.M., Ropke, C.D., 2008. Padronização e determinação da fotoestabilidade do extrato de folhas de *Pothomorphe umbellata* L. Miq. (Pariparoba) e aviliação da inhibição *in vitro* de metaloproteinases 2 e 9 na pele. Brazilian Journal of Pharmaceutical Sciences 44, 43–50.

Amorim, C.Z., Flores, C.A., Gomes, B.E., Marques, A.D., Cordeiro, R.S.B., 1988. Screening for antimalarial activity in the genus *Potomorphe*. Journal of Ethnopharmacology 24, 101–106.

Andrade, N.S., Souza, M.R., Perazzo, F.F., Bastos, J.K., Maistro, E.L., 2005. Evaluation of the mutagenic potential of a water-ethanolic extract of *Pothomorphe umbellata* (Piperaceae) aerial parts on Wistar rats cells by the Comet and Micronucleus assay. Cytologia 70, 399–405.

Andrade-Neto, V.F., Pohlit, A.M., Pinto, A.C., Silva, A.C.C., Nogueira, K.L., Melo, M.R.C., Nunomura, R.C.S., Nunomura, S.M., Alecrim, W.D., Alecrim, M.G.C., Chaves, F.C.M., Vieira, P.P.R., 2007. *In vitro* inhibition of *Plasmodium falciparum* by substances isolated from Amazonian antimalarial plants. Memórias do Instituto Oswaldo Cruz 102, pp. 359–365.

Anonymous, 1976. Unpublished data. National Cancer Institute. National Cancer Institute Central Files, EE.UU.

Anonymous, 1979. Consultation on Potentials for use of plants indicated by traditional medicine in diabetes mellitus and cardiovascular diseases. WHO, Ginebra, Switzerland, Oct. 30–Nov. 2.

Anonymous, 1988. WHO and traditional medicine. Bulletin of the World Health Organization 66, 266–267.

Anonymous, 2004. Use of *Pothomorphe umbellata* extract, composition on basis of *Pothomorphe umbellata* extract and method of application of the *Pothomorphe umbellata* extract. Publication number: WO2004026323 (A1), Publication date: 2004-04-01. Inventors: Barros Silvia Berlanga de Mora (Br); Ropke Cristina Dislich (Br), esp@cenet%20database.

Anonymous, 2007. International Classification of Diseases (ICD), 10th Revision. WHO Gineva, Switzerland.

Asprey, G.F., Thornton, P., 1954. Medicinal plants of Jamaica Part II. West Indian Medical Journal 3, 17–41.

Azevedo, S.K.deS., Silva, I.M., 2006. Plantas medicinais e religioso comercializadas em mercados e feiras livres no Rio de Janeiro, RJ, Brazil. Acta Botanica Brasilica 20, 185–194.

Barros, S.B.M., Teixeira, D.S., Aznar, A.E., Moreira Junior, J.A., Ishii, I., Freitas, P.C.D., 1996. Antioxidant activity of ethanolic extracts of *Pothomorphe umbellata* L. Miq. Ciência e Cultura (São Paulo) 48, 114–116.

Barros, S., Ropke, C.D., Sawada, T.C.H., Silva, V.V.D., Pereira, S.M.M., Barros, S.B.M., 2005. Assessment of acute and subchronic oral toxicity of ethanolic extract of *Pothomorphe umbellata* L. Miq. (Pariparoba). Brazilian Journal of Pharmaceutical Sciences 41, 53–61.

Barros, L.F.M., Barros, P.S.M., Ropke, C.D., Silva, V.V., Sawada, T.C.H., Barros, S.B.M., Belfort Jr., R., 2007. Dose-dependent *in vitro* inhibition of rabbit corneal matrix metalloproteinases by an extract of *Pothomorphe umbellata* after alkali injury. Brazilian Journal of Medical and Biological Research 40, 1129–1132.

Bergamo, D.C.B., Kato, M.J., Bolzani, V.D.S., Furlan, M., 2005. Biosynthetic origins of the isoprene units of 4-nerolidylcatechol in *Potomorphe umbellata*. Journal of the Brazilian Chemical Society 16, 1406–1409.

Bernhard, H.O., Thiele, K., 1978. Isolation of 1-allyl-2,3-dimetoxi-4,5-metillenodioxibenzeno from *Heckeria umbellata* (Piperaceae). Helvetica Chimica Acta 61, 2273.

Bidla, G., Titanji, V.P.K., Joko, B., El-Ghazali, G., Bolad, A., Berzins, K., 2004. Antiplasmodial activity of seven plants used in African folk medicine. Indian Journal of Pharmacology 36, 245–246.

Bioka, D., Abena, A., 1990. Psychopharmacological profile of *Piper umbellatum* aqueous extract. L'Encephale 16, 205–208.

Bodinga-bwa-Bodinga, Van der Veen, L., 1993. Plantes utiles des Evia: Pharmacopee. Pholia 8, 27–66.

Bonnelly, I., Vázquez, T.M., Terrero, D., 1985. Aspectos Químicos y Usos Nativos de Plantas en la Medicina Folklórica Dominicana. Universidad Autónoma de Santo Domingo, CIBIMA, Santo Domingo, Dominican Republic.

Bouquet, A., Debray, M., 1974. Medicinal plants of the Ivory Coast. Travail Document Orstom 32, 1.

Braga, F.G., Bouzada, M.L.M., Fabri, R.L., Matos, M., de, O., Moreira, F.O., Scio, E., Coimbra, E.S., 2007. Antileishmanial and antifungal activity of plants used in traditional medicine in Brazil. Journal of Ethnopharmacology 111, 396–402.

Brandão, M.G.L., Zanetti, N.N.S., Oliveira, P., Grael, C.F.F., Santos, Lima, A.C.P., Monte-Mor, R.L.M., 2008. Brazilian medicinal plants described by 19th century European naturalists and in the official Pharmacopoeia. Journal of Ethnopharmacology 120, 141–148.

Britto, V.L.M.Q., Resende, R.F., Gouveia, N.M., Amaral, F.C., Teixeira, E.H.M., Pereira, W.P., Espíndola, F.S., 2007. Plantas medicinais e fitoterápicos no contexto da academia, governo e organizações da sociedade civil: exemplo de iniciativas populares no município de Uberãndia-MG. Revista de Educação Popular, Uberlândia 6, 93–101.

Brohem, C.A., Sawada, T.C.H., Massaro, R.R., Almeida, R.L., Rivelli, D.P., Ropke, C.D., Silva, V.V., de Lima, T.M., Curi, R., Barros, S.B.M., Maria-Engler, S.S., 2009. Apoptosis induction by 4-nerolidylcatechol in melanoma cell lines. Toxicology in Vitro 23, 111–119.

Browner, C.H., 1985. Plants used for reproductive health in Oaxaca, Mexico. Economic Botany 39, 482–504.

Chartol, A., 1964. An insect repellent derived from *Piper umbellatum*. Medecine Tropicale 24, 743–747.

Chenu, J., 1986. Plantes medicinales des Antilles. Dajani Editions, West Indies.

Coelho, M.F.B., Silva, A.C. da Plantas de uso medicinal nos municípios de Pontes e Lacerda e de Comodoro, Mato Grosso, Brasil. http://www.ufmt.br/agtrop/revista7/doc/05.htm (acc. 07/04/08), in press.
Coelho, M.F.B., Azevedo, R.A.B., Casalia, V.W.D., Santos, R.H.S., 2002. Medicinal plants in the neighborhood of Serra do Brigadeiro State Park, Minais Gerais State, Brazil. Acta Horticulturae 569, 73–77.
Cordero, A.B., 1986. Manual de Medicina Domestica, Plantas Medicinales Dominicanas (2da edition). Publicaciones de la Universidad Autónoma de Santo Domingo, Vol. CCLII. Colección Ciencia y Tecnología no. 7, Santo Domingo, Dominican Republic.
Cos, P., Vlietinck, A.J., Vanden Berghe, D., Maes, L., 2006. Anti-infective potential of natural products: How to develop a stronger in vitro 'proof-of-concept'. Journal of Ethnopharmacology 106, 290–302.
Davis, M.E., 1987. La otra ciencia. El Vodú dominicano como religión y medicina popular. Edit. Universitaria Universidad Autónoma de Santo Domingo, Vol. DLXXVI, Santo Domingo, Dominican Republic.
De Oliveira, F., Akisue, G., 1984. Chromatographic characterization of the crude drug and fluid extract of *Pothomorphe umbellata* (L.) Miq. Anais de Farmacia e Quimica de São Paolo 24, 1–9.
Deive, C.E., 1981. Medicina y Farmacopea en Santo Domingo en el Siglo XVI. Aula (UNPHU, Santo Domingo) 39, 71–84.
Deive, C.E., 1992. Vodu y Magia en Santo Domingo, Tercera Ed. Fundación Cultural Dominicana, Santo Domingo, Dominican Republic.
Desmarchelier, C., Barros, S., Repetto, M., Latorre, L.R., Kato, M., Coussio, J., Ciccia, G., 1997. 4-Nerolidylcatechol from *Pothomorphe* spp. scavenges peroxyl radicals and inhibits Fe(II)-dependent DNA damage. Planta Medica 63, 561–563.
Di Stasi, L.C., Oliveira, G.P., Carvalhaes, M.A., Queiroz-Junior, M., Tien, O.S., Kakinami, S.H., Reis, M.S., 2002. Medicinal plants popularly used in the Brazilian Tropical Atlantic Forest. Fitoterapia 73, 69–91.
Díaz, W., Ortega, F., 2006. Inventario de recursos botánicos útiles y potenciales de la Cuenca del río Morón, Estado Carabobo, Venezuela. Ernestia 16, 31–67.
Domis, M., Oyen, L.P.A., 2008. *Piper umbellatum* L. In: Prota Base Record Display, PROTA, Plant Resources of Tropical Africa. www.prota.org (accessed: 11/12/2008).
Estrella, E., 1995. Plantas medicinales amazónicas: Realidad y perspectivas. Tratado de Cooperación Amazónica, Secretaría Pro-Tempore, Lima, Peru.
Farnsworth, N.R., Akerele, O.A.S., Soejarto, D.D., Guo, Z., 1985. Medicinal plants in therapy. Bulletin of the World Health Organization 63, 965–981.
Farnsworth, N.R., Loub, W.D., 1983. Information gathering and data bases that are pertinent to the development of plant-derived drugs. In: Plants: The potentials for extracting protein, medicines, and other useful chemicals-Workshop Proceedings. (Washington, D.C.; U.S. Congress, Office of Technology Assessment, OTA-BP-F-23, September 1983).
Felzenszwalb, I., Valsa, J.O., Araujo, A.O., Alcantara-Gomes, R., 1987. Absence of mutagenicity of *Pothomorphe umbellata* and *Pothomorphe peltata* in the *Salmonella*/mammalian microsome mutagenicity assay. Brazilian Journal of Medicine and Biological Research 20, 403–405.
Fenner, R., Heemann Betti, A., Auler Mentz, L., Kuze Rates, S.M., 2006. Plantas utilizadas na medicina popular brasileira com potencial atividade antifúngica. Brazilian Journal of Pharmaceutical Sciences 42, 369–394.
Ferreira-da-Cruz, M.F., Adami, Y.L., Espinola-Mendes, E.C., Figueiredo, M.R., Daniel-Ribeiro, C.T., 2000. The intraperitoneal *Plasmodium berghei* – Pasteur infection of Swiss mice is not a system that is able to detect the antiplasmodial activity in the *Pothomorphe* plant extracts that are used as antimalarials in Brazilian endemic areas. Experimental Parasitology 94, 243–247.
Germosén-Robineau, L., 1995. Hacia una farmacopea Caribeña, edición TRAMIL 7. Enda – Caribe, UAG & Universidad de Antioquía, Santo Domingo, Dominican Republic.
Gertsch, J., 2009. How scientific is the science in ethnopharmacology? Historical perspectives and epistemological problems. Journal of Ethnopharmacology 122, 177–183.
Gertsch, J., Leonti, M., Raduner, S., Racz, I., Chen, J.-Z., Xie, X.-Q., Altmann, K.-H., Karsak, M., Zimmer, A., 2008. Beta-caryophellene is a dietary cannabinoid. Proceedings of the National Academy of Science (USA) 105, 9099–9104.
Grandi, T.S.M., Trindade, J.A., Pinto, M.J.F., 1989. Plantas medicinais de Minais Gerais, Brasil. Acta Botanica Brasilica 3, 185–224.
Grieve, M. A Modern Herbal. http://botanical.com/botanical/mgmh/p/pepper24.html (accessed: 26/11/2008), in press.
Hammer, M.L.A., Johns, E.A., 1993. Tapping an Amazonian plethora: four medicinal plants of Marajó Island, Pará, (Brazil). Journal of Ethnopharmacology 40, 53–75.
Hazlett, D.L., 1986. Ethnobotanical observations from Cabecar and Guaymí settlements in Central America. Economic Botany 40, 339–352.
Hegnauer, R., 1969. Chemotaxonomie der Pflanzen V. Birkhauser Verlag, Basel, Suiza.
Heinrich, M., Edwards, S., Moerman, D.E., Leonti, M., 2009. Ethnopharmacological field studies: a critical assessment of their conceptual basis and methods. Journal of Ethnopharmacology 124, 1–17.
Hoogte, L., van der, Roersch, C., 1984. Perspectivas de la Medicina Andina, Allpanchis nr. 24, año XIV, Vol. XX, pp. 155–182.
Hoogte, L., van der Roersch, C., 1988. Atención Primaria y Medicina Tradicional, sus Alcances y nuestros limites. In: Roersch, C., Van der Hoogte, L., Tavares de Andrade, J.M. (Eds.), La Medicina Tradicional en Sistemas Formales de Salud. Centro de Medicina Andina, Cusco, Peru, pp. 119–146.
IMD (Instituto de Medicina Dominicana), Equipo Pastoral de la Diócesis de Baní, Grupo 'Somos una Flor', 1994a. Algunas enfermedades con su tratamiento tradicional de la comunidad rural 'La Montería', Bani. In: IMD (Ed.), Santo Domingo, Dominican Republic.
IMD (Instituto de Medicina Dominicana), Dep. de Salud de la Junta de Desarrollo de San José de Ocoa, Grupo 'Luz y Vida', 1994b. Algunas enfermedades con su tratamiento tradicional de la comunidad rural 'La Cienaga', de San José de Ocoa. In: IMD (Ed.), Santo Domingo, Dominican Republic.
IMD (Instituto de Medicina Dominicana), Dep. de Salud de la Junta de Desarrollo de San José de Ocoa, Grupo 'Flor de Libertad', 1994c. Algunas enfermedades con su tratamiento tradicional de la comunidad rural 'Bayona', San José de Ocoa. In: IMD (Ed.), Santo Domingo, Dominican Republic.
IMD (Instituto de Medicina Dominicana); Dep. de Salud de la Junta de Desarrollo de San José de Ocoa, Grupo 'Nuevo Amanecer', 1997. Algunas enfermedades con su tratamiento tradicional de la comunidad rural 'Los Ranchitos', San José de Ocoa. In: IMD (Ed.), Santo Domingo, Dominican Republic.
IMD (Instituto de Medicina Dominicana), Caritas Diocesana de Bani, Grupo de Mujeres 'Somos una Flor', 1999. Plantas Medicinales usadas en varias enfermedades en la comunidad de 'La Montería', Baní, Prov. Peravia. In: IMD, Caritas Diocesana (Eds.), Santo Domingo, Dominican Republic.
IMD (Instituto de Medicina Dominicana), Caritas Diocesana de Bani, Grupo de Mujeres 'Accion Comunitaria Las Tablas', 1999. Experiencias con Plantas Medicinales en la comunidad 'Las Tablas', Baní. In: IMD, Caritas Diocesana (Eds.), Santo Domingo, Dominican Republic.
IMD (Instituto de Medicina Dominicana), Fundación Loma Quita Espuela, Grupo 'Mujeres Unidas', 1999. Plantas Medicinales usadas en varias enfermedades en la comunidad de Naranja Dulce, San Francisco de Macorís. In: IMD, Fundación Loma Quita Espuela (Eds.), Santo Domingo, Dominican Republic.
IMD (Instituto de Medicina Dominicana), Fundación Loma Quita Espuela, grupo Medicina Tradicional Dominicana 'La Bajada', 1999. Plantas medicinales usadas en varias enfermedades en la comunidad de La Bajada, San Francisco de Macorís. In: IMD, Fundación Loma Quita Espuela (Eds.), Santo Domingo, Dominican Republic.
Isobe, T., Ohsaki, K., Nagaka, K., 2002. Antibacterial constituents against *Helicobacter pylori* of Brazilian medicinal plant, Pariparoba. Yakugaku Zasshi 122, 291–294.
Jiofack, T., Fokunang, C., Kemeuze, V., Fongnzossie, E., Tsabang, N., Nkuinkeu, R., Mapongmetsem, P.M., Nkongmeneck, B.A., 2008. Ethnobotany and phytopharmacopoea of the South-West ethnoecological region of Cameroon. Journal of Medicinal Plant Research 2, 197–206.
Kamanzi Atindehou, K., Schmid, C., Brun, R., Koné, M.W., Traore, D., 2004. Antitrypanosomal and antiplasmodial activity of medicinal plants from Côte d'Ivoire. Journal of Ethnopharmacology 90, 221–227.
Kaou, A.M., Mahiou-Leddet, V.M., Hutter, S., Aïnouddine, S., Hassani, S., Yahaya, I., Azas, N., Ollivier, E., 2008. Antimalarial activity of crude extracts from nine African medicinal plants. Journal of Ethnopharmacology 116, 74–83.
Kashanipour, R.A., McGee, R.J., 2004. Northern Lacandon Maya Medicinal Plant use in Communities of Lacanja Chan Sayab and Naha, Chiapas, Mexico. Journal of Ecological Anthropology 8, 47–66.
Kerharo, J., Bouquet, A., Debrey, A., 1950. Plantes medicinales et toxiques de la Côte-d'Ivoire – Haute-Volta. Vigot Freres, Paris, France.
Kijjoa, A., Giesbrecht, A.M., Akisue, M.K., Gottlieb, O.R., Gottlieb, H.E., 1980. 4-Nerolidylcatechol from *Pothomorphe umbellata*. Planta Medica 39, 85–87.
Kokwaro, J., 1976. Medicinal Plants of East Africa. East African Literature Bureau, Nairobi, Ethiopia.
Kuschick, I., 1995. Medicina Popular en España. Siglo Veitiuno Editores, Spain.
Lajide, L., Adedire, C.O., Muse, W.A., Agele, S.O., 1998. Insecticidal activity of powders of some Nigerian plants against the maize weevil (*Sitophilus zeamais* Mots). Entomology in the Nigerian economy. Research focus in the 21st century. Entomological Society of Nigeria, Maiduguri, Nigeria, pp. 227–235.
Le Grand, A., Sri-Ngernyuang, L., 1989. Herbal Drugs in Primary Health Care: Thailand: The Impact of Promotional Activities on Drug Consumption, Drug Provision and Self-Reliance. Royal Tropical Institute, Amsterdam, The Netherlands.
Liogier, A.H., 1990. Plantas Medicinales de Puerto Rico y del Caribe. Iberoamericana Ediciones, Hato Rey, Puerto Rico.
Liogier, A.H., 2000. Diccionario Botánico de Nombres Vulgares de la Española, 2de Edición. Jardín Botánico "Dr. Rafael M. Moscoso" y Universidad Nacional Pedro Henriquez Ureña, Santo Domingo, Dominican Republic.
Luz, A.I.R., Da-Silva, J.D., Zoghbi, M.G.B., Andrade, E.H.A., Da-Silva, M.H.L., Maia, J.G.S., 1999. Volatile constituents of Brazilian Piperaceae, Part 5. The oils of *Pothomorphe umbellata* y *P. peltata*. Journal of Essential Oil Research 11, 479–481.
Maia, J.G.S., Andrade, E.H.A., 2009. Database of the amazon aromatic plants and their essential oils. Quimica Nova 32, 595–622.
Mañon, D.I., Haché, Ll.I., García, S.E., 1992. Medicina Tradicional Dominicana (una contribución a su estudio). Universidad Nacional Pedro Henríquez Ureña, Academia Dominicana de Medicina, Museo del Hombre Dominicana, Instituto Dominicano de Ambiente y Sociedad, Santo Domingo, Dominican Republic.
Martins, A.P., Salguiero, L., Vila, R., Tomi, F., Cañigueral, S., Casanova, J., Proença Da Cunha, A., Adzett, T., 1998. Essential oils from four *Piper* species. Phytochemistry 49, 2019–2023.
Mensah, J.K., Okoli, R.I., Ohaju-Obodo, J.O., Eifediyi, K., 2008. Phytochemical, nutricional and medicinal properties of some leafy vegetables consumed by Edo people of Nigeria. African Journal of Biotechnology 7, 2304–2309.
Mentz, L.A., Lutzemberger, L.C., Schenkel, E.P., 1997. Da flora medicinal do Rio Grande Do Sul: notas sobre obra de D'Ávila (1910). Caderno de Farmácia 13, 25–48.
Mesquita, J.M.O., Cavaleiro, C., Cunha, A.P., Lombardi, J.A., Oliveira, A.B., 2005. Estudo comparativo dos óleos voláteis de algumas espécies de Piperaceae. Brazilian Journal of Pharmacognosy 15, 6–12.
Mitchell, S.A., Ahmad, M.H., 2006. A review of medicinal plant research at the University of the West Indies, Jamaica, 1948–2001. West Indian Medical Journal 55, 243–269.

Moerman, D.E., 2007. Agreement and meaning: rethinking consensus analysis. Journal of Ethnopharmacology 112, 451–460.
Ndukwu, B.C., Ben-Nwadibia, N.B. Ethnomedical aspects of plants used as spices and condiments in the Niger delta area of Nigeria. http://www.siu.edu/~ebl/leaflets/niger.htm (accessed: 16-02-2009), in press.
Nkounkou-Loumpangou, C., Binimbi-Massengo, A., Nzonzi, J., Quamba, J.M., Abena, A.A., Diatewa, M., 2005. Inventaire des plantes médicinales utilisées dans le traitment de l'infertilité féminine à Brazzaville. Phytothérapie 6, 252–259.
Noriega, P., Ropke, C.D., Consiglieri, V.O., Taqueda, M.E.S., Tavares, L.C., Wasicky, A., Bacchi, E.M., Barros, S.B.M., 2008. Optimization of *Pothomorphe umbellata* (L.) Miquel topical formulations using experimental design. International Journal of Pharmaceutics 353, 149–159.
Noumi, E., Houngue, F., Lontsi, D., 1999. Traditional medicines in primary health care: plants used for the treatment of hypertension in Bafia, Cameroon. Fitoterapia 70, 134–139.
Noumi, E., Dibakto, T.W., 2000. Medicinal plants used for peptic ulcer in the Bangangte region, Western Cameroon. Fitoterapia 71, 406–412.
Noumi, E., Yomi, A., 2001. Medicinal plants used for intestinal diseases in Mbalmayo region, Central Province, Cameroon. Fitoterapia 72, 246–254.
Núñez, V., Castro, V., Murillo, R., Ponce-Soto, L.A., Merfort, I., Lomonte, B., 2005. Inhibitory effects of *Piper umbellatum* and *Piper peltatum* extracts towards myotoxic phospholipases A2 from *Bothrops* snake venoms: isolation of 4-nerolidylcatechol as active principle. Phytochemistry 66, 1017–1025.
Oliveira, F.Q., Junqueira, R.G., Stehman, J.R., Brandão, M.G.L., 2003. Potencial das plantas medicinais como fonte de novos antimaláricos: espécies indicadas na bibliografia etnomédica brasileira. Revista Brasileira de Plantas Medicinais, Botucatu 5, 23–31.
Ososki, A.L., Balick, M.J.L., Daly, D.C., 2007. Medicinal plants and cultural variation across Dominican Rural, Urban, and Transnational landscapes. In: Pieroni, A., Vandebroek, I. (Eds.), Traveling Cultures and Plants. The Ethnobiology and Ethnopharmacy of Human Migrations. Vol. 7. Studies in Environmental Anthropology and Ethnobiology, Vol. 7. Berghahn Books, New York, USA.
Peguero, B., Jiménez, F., Veloz, A., 2001. Estudio etnobotánico en el Cachote, provincia Barahona, República Dominicana. Moscosoa 12, 79–104.
Peguero, B., 2002. Estudio etnobotánico de las comunidades ubicadas dentro y en la periféria del Parque Nacional Juan Bautista Pérez Rancier (Valle Nuevo). In: Núñez, F., et al. (Eds.), Evaluación ecológica integrada del Parque Nacional Juan Bautista Pérez Rancier (Valle Nuevo). Secretario de Medio Ambiente y Recursos Naturales y la Fundación Moscoso Puello, Santo Domingo, Dominican Republic.
Perazzo, F.F., Souza, G.H.B., Lopes, W., Cardoso, L.G.V., Carvalho, J.C.T., Nanayakkara, N.P.D., Bastos, J.K., 2005. Anti-inflammatory and analgesic properties of water-ethanolic extract from *Pothomorphe umbellata* (Piperaceae) aerial parts. Journal of Ethnopharmacology 99, 215–220.
Pino, J.A., Marbot, R., Fuentes, V., Payo, A., Chao, D., Herrera, P., 2005. Aromatic plants from Western Cuba. II. Composition of leaf oil of *Pothomorphe umbellata* (L.) Miq. and *Ageratina havanensis* (H.B.K.) R.M. Kinget. Journal of Essential Oil Research 17, 572–574.
Pohle, P., Reinhardt, S., 2004. Indigenous knowledge of plants and their utilization among the Shuar of the lower tropical mountain forest in southern Ecuador. Lyonia 7, 133–149.
Polanco, D., Peguero, B., Jiménez, F., 1998. Estudio etnobotánico en siete comunidades rurales de Bayaguana, Republica Dominicana. Moscosoa 10, 86–113.
Polygenis-Bigendako, M.J., 1990. Recherches ethnopharmacognosiques sur les plantes utilisées en médecine traditionelle au Burundi occidental. Thèses de Docteur en Sciences, Univ. Libre de Bruxelles, Fac. Sc., Lab. de Botanique Systématique et de Phytosociologie. In: Krief, S., Hladik, C.M., Haxaire, C., 2005. Ethnomedicinal and bioactive properties of plants ingested by wild chimpanzees in Uganda. Journal of Ethnopharmacology 101, 1–15.
Reiff, M., O'Conner, B., Kronenberg, F., Balick, M., Lohr, P., Roble, M., Fugh-Berman, A., Johnson, K.D., 2003. Ethnomedicine in the urban environment: Dominican Healers in New York City. Human Organization 62, 12–26.
Robinson, G.G., López, B., 1999. Medicinal plants use patterns among the Amuzgos of Guerrero, México. http://www.sil.org/mexico/amuzga/guerrero/A006i-MedicinalPlants-AMU.pdf (accessed: 16-12-2008).
Rodrigues, A.C.C., Guedes, M.L.S., 2006. Utilização de plantas medicinais no Povoado Sapucaia, Cruz das Almas – Bahia. Revista Brasileira de Plantas Medicinais, Botucatu 8, 1–7.
Roersch, C., 1994. Plantas Medicinales en el Sur Andino del Perú. Koeltz Scientific Books, Koenigstein, Alemania.
Roersch, C., 1995. Plantas medicinales: medicamentos o no? Cuadernos IMD, Serie Plantas Medicinales, no. 3. Santo Domingo.
Roersch, C., 1999. The Marketing of Medicinal Plants, Aromatic Plants and Essential Oils in the Dominican Republic. Presented at: II World Congress on Medicinal and Aromatic Plants for Human Welfare. 10–15 Nov. 1997, Mendoza, Argentina. Published in: Acta Horticulturae 503, pp. 197–219.
Roersch, C., Hoogte, L., van der., 1987. Un intento de usar la Medicina Tradicional en la atención de la Salud en Perú: El caso del Sur Andino. In: El Futuro de la Medicina Tradicional en la Atención a la Salud de los Países Latinoamericanos. Centro Interamericano de Estudios de Seguridad Social 'Jesús Reyes Heroles' Mexico, pg. 91–106.
Roig, J.T., 1945. Plantas medicinales, aromáticas y venenosas de Cuba. Ministerio de Agricultura, Havanna, Cuba.
Ropke, C.D., Meirelles, R.R., Silva, V.V., Sawada, T.C.H., Barros, S.B.M., 2003. *Pothomorphe umbellata* extract prevents alfa-Tocopherol depletion after UV-irradiation. Photochemistry and Photobiology 78, 436–439.
Ropke, C.D., Sawada, T.C.H., Silva, V.V., Michalany, N.S., Barros, S.B.M., 2005. Photoprotective effect of *Pothomorphe umbellata* root extract against ultraviolet radiation induced chronic skin damage in the hairless mouse. Clinical and Experimental Dermatology 30, 272–276.
Ropke, C.D., Silva, V.V., Kera, C.Z., Miranda, D.V., Almeide, R.L., Sawada, T.C.H., Barros, S.B.M., 2006. *In vitro* and *in vivo* inhibition of skin matrix metalloproteinases by *Pothomorphe umbellata* root extract. Photochemistry and Photobiology 82, 439–442.
Sacoman, J.L., Monteiro, K.M., Possenti, A., Figueira, G.M., Foglio, M.A., Carvalho, J.E., 2008. Cytotoxicity and antitumoral activity of dichloromethane extract and its fractions from *Pothomorphe umbellata*. Brazilian Journal of Medical and Biological Research 41, 411–415.
Santos, M.R.A., Lima, M.R., 2008. Levantamento dos recursos vegetais utilizados como fitoterápicos no município de Cujubim, Rondõnia, Brasil. Saber Científico 1, 58–74.
Saralegui, H., 2004. Piperaceae. In: Greuter, W., Rankin Rodriguez, R. (Eds.), Flora de la República de Cuba, Series A: Plantas vasculares. Fasc. 09, Min. de Educación Superior, Havanna, Cuba.
Schmelzer, G.H., 2001. *Piper umbellatum* L. In: van Valkenburg, J.L.C.H., Bunyapraphatsara, N. (Eds.), Plant Resources of South-East Asia No. 12(2): Medicinal and Poisonous Plants 2. Backhuys Publishers, Leiden, The Netherlands.
Schultes, R.E., 1980. De Plantes Toxicariis e Mundo Novo Tropicale Commentation. XXVI. Ethnopharmacological notes on the flora of Northwestern South America. Botanical Museum Leaflet Harvard University 28, 1–45.
Schultes, R.E., Raffauf, R.F., 1990. The healing forest – medicinal and toxic plants of the northwest Amazonia. Historical, ethno- and economic botany series, Vol. 2. Dioscorides Press, Portland, Oregon.
Sen, C.K., Khanna, S., Gordillo, G., Bagchi, D., Bagchi, M., 2002. Oxygen, oxidants, and antioxidants in wound healing: an emerging paradigm. Annals of the New York Academy of Sciences 957, 239–249.
Sequeira, V., 1994. Medicinal plants and conservation in São Tomé. Biodiversity and Conservation 3, 910–926.
Soneja, A., Drews, M., Malinski, T., 2005. Role of nitric oxide, nitroxidative and oxidative stress in wound healing. Pharmacological Reports 57, 108–119.
Stehmann, J.R., Brandão, M.G.L., 1995. Medicinal Plants of Lavras Novas (Minas Gerais, Brazil). Fitoterapia 56, 515–520.
Tabopda, T.K., Ngoupayo, J., Liu, J., Mitaine-Offer, A.C., Tanoli, S.A.K., Khan, S.N., Ali, M.S., Ngadjui, B.T., Tsamo, E., Lacaille-Dubois, M.A., Luu, B., 2008. Bioactive aristolactams from *Piper umbellatum*. Phytochemistry 69, 1726–1731.
Trotter, R.T., Logan, M.H., 1986. Informant consensus: a new approach for identifying potentially effective medicinal plants. In: Etkin, N.L. (Ed.), Plants in Indigenous Medicine and Diet. Biobehavioral Approaches. Redgrave Publishing Co., Bedford Hills, NY, pp. 91–112.
Valadares, M.C., Rezende, K.R., Pereira, E.R.T., Sousa, M.C., Gonçalves, B., Asis, J.C., Kato, M.J., 2007. Protective effects of 4-nerolidylcatechol against genotoxicity induced by cyclophosphamide. Food and Chemical Toxicology 45, 1975–1978.
Vandebroek, I., Balick, M.J., Yukes, J., Duran, L., Kronenberg, F., Wade, C., Ososki, A.L., Cushman, L., Lantigua, R., Mejia, M., Robineau, L., 2007. Use of medicinal plants by Dominican immigrants in New York City for the treatment of common health conditions. A comparative analysis with literature data from the Dominican Republic. In: En: Pieroni, A., Vandebroek, I. (Eds.), Traveling Cultures and Plants. The Ethnobiology and Ethnopharmacy of Human Migrations. Vol. 7. Studies in Environmental Anthropology and Ethnobiology. Berghahn Books, New York, USA.
Vasileva, B., 1969. Plantes medicinales de Guinee, Conakry (Republique de Guinee). University of Moscow, Russia.
Viana, V.R.C., Tavares, E.S., De Matos Alves, H., Simoes, C., Albarello, N., Lua, F., Solange, F., 2000. In Vitro propagation of *Pothomorphe umbellata* to obtain 4-nerolidylcatechol producing clones. Revista Brasileira de Farmacia 81, 43–47.
Vieira, R.F., Martins, M.V.M., 2000. Recursos genéticos de plantas medicinais do Cerrado: uma compilação de dados. Revista Brazileira de Plantas Medicinais, Botucatu 3, 13–36.
Vogler, B., Noletto, J.A., Haber, W.A., Setzer, W.N., 2006. Chemical constituents of the essential oils of three *Piper* species from Monteverde, Costa Rica. Journal of Essential Oil-Bearing Plants 9, 230–238.
Werka, J.S., Boehme, A.K., Setzer, W.N., 2007. Biological activities of essential oils from Monteverde, Costa Rica. Natural Product Communications 2, 1215–1219.
WHO, 1978. Primary Health Care. Report of The International Conference on Primary Health Care, Alma – Ata, U.S.S.R., Sept. 6–12. "Health for All" Series, No. 1, WHO, Geneva, Switzerland.
WHO, 2002. Traditional Medicine Strategy 2002–2005. WHO/EDM/TRM/2002.1, Geneva, Switzerland.
Wondergem, P., Senah, K.A., Golver, E.K., 1989. Herbal Drugs in Primary Health Care: Ghana: An Assessment of the Relevance of Herbal Drugs in PHC and Some Suggestion for Strengthening PHC. Royal Tropical Institute, Amsterdam, The Netherlands.
Yamada, T., 1999. A report on the ethnobotany of the Nyindu in the Eastern part of the former Zaire. African Study Monographs 20, 1–72.
Zamora-Martínez, M.C., Pola, C.N.P., 1992. Medicinal plants used in some rural populations of Oaxaca, Puebla and Veracruz, Mexico. Journal of Ethnopharmacology 35, 229–257.