10

Zanthoxylum Genus as Potential Source of Bioactive Compounds

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1. Introduction

Natural products have been used for thousands of years for the benefit of mankind, as important sources of food, clothing, cosmetics, building materials, tools, medicines and crop protection agents. They have made enormous contributions to human health through compounds such as quinine, morphine, aspirin (a natural product analog), digitoxin and many others. Researches in this field are becoming more numerous, to the point of getting about half of pharmaceuticals and pesticides from natural sources (Newman & Cragg, 2007). The main reasons because natural products are so important to undertake research are that they can be a source of new compounds because they produce many bioactive secondary metabolites that are used as a chemical defense against predators. Also, in the past, they have provided many new drugs, some of which can't be obtained by other sources and because they can provide the necessary templates to design new products in the future (Colegate and Molyneux, 2008; Kaufman et al., 2006; Cragg et al., 2005).

Dissatisfied therapeutic needs in the treatment of bacterial, parasitic, viral and fungal infections, cancer, Alzheimer's and AIDS, among other diseases, have led to the search of new substances with therapeutic applications. Although for most diseases there is a treatment, many of them have begun to be ineffective due to the development of resistance to medicaments that were initially effective and to the low security that they exhibit for patients. Consequently, the development of effective and safe therapeutic alternatives is essential to ensure the availability of new products that reduce mortality and morbidity due to diseases (Pan et al., 2010; Nwaka & Hudson, 2006; Segal & Elad, 2006; Waldvogel, 2004).

The search for new phytosanitary agents to control plant pests and diseases that affect many plant sources of food and/or industrial use is also of great interest, because the indiscriminate and permanent use of agrochemicals has led to the emergence of resitant pests and phytopathogenic microorganisms, that can cause partial or complete loss of crops (Agrios, 2005; Strand, 2000).

Research in plants represents an invaluable source discovering new substances, considering that each of these can contain hundreds or even thousands of secondary metabolites. From the 250,000 to 300,000 plant species reported, only a small part has been the subject of phytochemical and biological activity studies (Tringali, 2001).

This chapter shows information about the importance of ethnobotany, phytochemistry and biological activities of species of the genus *Zanthoxylum*, information that can be the base for undertaking future research.

2. Overview of *Zanthoxylum* genus

Zanthoxylum genus belongs to the Rutaceae family. It is economically important because of their alimentary, industrial and medicinal applications (Seidemann, 2005; Chase et al., 1999). *Zanthoxylum* comes from the word *Xanthoxylum* wich derives from Greek: "xanthon xylon" that means "yellow wood", hence the use of the terms *Xanthoxylum* or *Zanthoxylum* by some authors. The genus *Zanthoxylum* was created by Linné in 1757 and since its inception has been confused with the genus *Fagara*. In 1896, Engler made the distinction between the two genera by the following characteristics: species of the genus *Zanthoxylum* have a simple perianth, while in species of the genus *Fagara* is twofold. Brizicky in 1962, discovered some species with intermediate perianth, which showed that simple perianth of *Zanthoxylum* drift from the *Fagara* due to failure of some sepals, and concluded that *Fagara* and *Zanthoxylum* genus are the same. Finally, in 1966, Hartley grouped *Zanthoxylum* and *Fagara* under the name of *Zanthoxylum*. However, some authors still use the term *Fagara* (Chaaib, 2004).

Zanthoxylum comprises about 549 species distributed worldwide mainly in tropical and temperate regions (Global Biodiversity Information Facility, 2010). This genus includes trees and shrubs, usually dioecious. The trees have leafy crown, with few branches and reach up to 20 meters. The species of this genus are characterized by the presence of recurved spines on its trunk and branches. The leaves are varied, may be alternate or opposite, simple or composed, imparipanadas or parimpanadas with up to 15 pairs of leaflets. The inflorescences are usually in form of panicles or umbels compound, axillary or terminal of small flowers. The flowers are actinomorphic, hermaphrodite and unisexual, rarely bisexual, usually white or green. The fruits are follicles or esquizocarp, contains from one to five carpels usually aromatic, and the are ordinarily bivalve with a single red or black, shiny seeds (Melo & Zickel, 2004; Silva & Paoli, 2004).

The genus *Zanthoxylum* has great importance due to its ethnobotanics, phytochemistry and biological activity, and it is a promising source of various secondary metabolites including benzophenanthridine alkaloids.

3. Ethnobotanical uses

Species of this genus are of economic importance as sources of edible fruits, oils, wood, raw materials for industries, medicinal plants, ornamentals, culinary applications, and are characterized by a satin wood commonly used in woodworking (Yang, 2008; Da Silva *et al.*, 2006; Adesina, 2005; Seidemann, 2005). For example in Africa is used the wood of *Z. gillettii*, *Z. tessmannii*, *Z. lemairei* and *Z. leprieurii* for houses, buildings, drums and ships construction, and for decorative woodwork, carpentry, and paper industry. In some countries of this continent, root bark and stem of many species of *Zanthoxylum* for used as a vermifuge, febrifuge and piscicides (Adesina, 2005).

Zanthoxylum species are also used in the field of perfumery and food industry because of its essential oils from leaves, fruits and inflorescences. The most used essential oils are obtained

from *Z. xanthoxyloides* (Ngassoum et al., 2003), *Z. gillettii* (Jirovetz et al., 1999) and *Z. simulans* (Chyau et al., 1996).

A common feature of almost all species of the genus *Zanthoxylum* is the ability to produce tires, which could be used in the pharmaceutical industry as encapsulants, emulsifying agents or diluents. Some investigations have been conducted on the rubber collected on the bark of *Z. tessmannii* (Adesina, 2005).

Many species of the *Zanthoxylum* genus have been used in different parts of the world especially in Asia, Africa and America to treat a number of diseases in humans and animals (McGaw et al., 2008; Rochfort et al., 2008; Adesina, 2005; Chaaib, 2004; Diéguez et al., 2004; Patiño, 2004). For example, the bark of *Z. integrifolioum* is used in traditional medicine by Ya-Mei and Lanyu indigenous tribes in Taiwan, as a remedy for snakebite, dyspepsia and as an aromatic tonic for fever. The bark of *Z. liebmannianum*, is used in Mexico for the treatment of stomach pains, amebiasis, intestinal parasites and as a local anesthetic agent (Ross et al., 2004). Some species are used for the treatment of malaria, such is the case of *Z. rhoifolium* (Jullian et al., 2006; Bertani et al., 2005), *Z. acutifolium* (Arruda et al., 1992), *Z. chalybeum* (Jullian et al., 2006) and *Z. usambarense* (Kirira et al., 2006). Venezuelan traditional medicine is known to use *Z. monophyllum* in the treatment of runny nose or nasal mucosal inflammation, jaundice, ophthalmia and as an anesthetic (Gomez et al., 2007; Diaz & Ortega, 2006). Another use has been given as a textile dye (De Garcia et al., 1989).

According to reports of ethnobotanical properties of the *Zanthoxylum* genus, in general it is emphasized that the most commonly used extraction methods are infusion and decoction, using mainly water as solvent. In Table 1 are summarized the main ethnobotanical uses of 45 species of the genus *Zanthoxylum*, as well as the plant part used and method of preparation. The major ethnobotanical properties attributed to these plant species are: relief of dental problems, treatment of malaria, gastrointestinal disorders, gonorrhea and lung diseases, antidiarrheal use in animals and humans, emmenagogue action, effective for rheumatism, anthelmintic use in animals and humans, aphrodisiac, analgesic, action against various skin diseases, febrifuge, antihemorrhagic, effective for genitourinary diseases, anticancer, diuretic, stomachic, anti-convulsive, tonic and stimulant. In addition to the medicinal properties, some species are also used as pesticides, building materials and textile dyes.

Some plants have been used as components of natural medicines, because of the important ethnomedical properties of *Zanthoxylum* genus species. *Z. tingoassuiba* has been marketed since 1923 by Flora Medicinal J. Monteiro da Silva Laboratory, as part of herbal medicinal product called Uva do Mato®, which is prescribed for muscle cramps and spasms (Da Silva et al., 2008). *Z. rhoifolium* also has been commercialized in Brazil as a component of herbal tea mixtures sold in drugstores, supermarkets and popular markets (Pereira et al., 2010; Da Silva et al., 2007a).

4. Phytochemistry

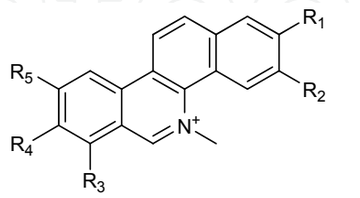
Phytochemical studies carried out on species of the genus *Zanthoxylum*, alkaloids of various types, lignans, coumarins amides are commonly secondary metabolites reported and have chemotaxonomic importance to the genre. Also, other metabolites have been isolated such as flavonoids, sterols and terpenes, among others (Adesina, 2005; Patiño, 2004, Waterman & Grundon, 1983).

4.1 Alkaloids

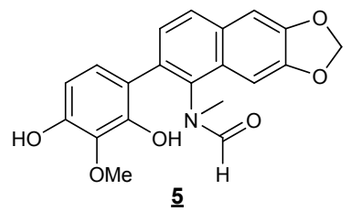
The alkaloids are most important compounds for the genus *Zanthoxylum*, because they are present in most species and have been found in all plant organs, being abundant in the trunk and root bark (Dieguez et al., 2004). The main isolated alkaloids from the genus are of two types: isoquinolines (benzophenanthridine, benzylisoquinoline, aporphine, protoberberine and berberine) and quinolines (Krane et al. 1984; Waterman & Grundon, 1983; Cordell, 1981). Other types of alkaloids have also been found in some species of the genus.

4.1.1 Isoquinoline alkaloids

The **benzophenanthridines** are the most frequently reported type of alkaloid in the genus *Zanthoxylum* and have great interest due to important and varied biological activity that they present, among which highlights the antitumor activity (Maiti & Kumar, 2009; Tillequin, 2007; Maiti & Kumar, 2007; Dvorak et al., 2006; Nyangulu et al., 2005; Eun & Koh, 2004; Tang et al. 2003; Slaninová et al., 2001; Simeon et al., 1989). Representatives of these alkaloids have exhibited antimalarial (Nyangulu et al., 2005; Ross et al., 2004), antileukemic (Dupont et al., 2005), antioxidant (Pérez et al., 2003), nematicide (Matsuhashi et al., 2002), HIV (Chang et al., 2003), antibacterial (Gonzaga et al., 2003), antimicrobial (Nissanka et al., 2001) and antifungal activities (Queiroz et al., 2006), among others. Their distribution is very limited in plants, and only they have been isolated from some genera belonging to the families Papaveraceae, Rutaceae and Fumiraceae mainly, where they are considered chemotaxonomic markers. In Rutaceae family they are present in species of the genera *Phellodendron*, *Fagaropsis*, *Tetradium*, *Toddalia* and *Zanthoxylum* (including *Fagara*), the latter with a majority presence of these alkaloids from the others (Krane et al., 1984; Cordell, 1981). The main representatives of this type of alkaloids are fagaronine **1**, nitidine **2**, chelerythrine **3** and sanguinarine **4**. Compounds with similar chemical structure to iwamide **5** and integriamide **6**, isolated from various species of the genus *Zanthoxylum*, have been classified by different authors within benzophenanthridine alkaloids (Krane et al., 1984).



1: R_1 = OH; R_2 = OMe; R_3 = H; R_4 = R_5 = OMe
2: $R_1 + R_2 = OCH_2O$; R_3 = H; R_4 = R_5 = OMe
3: $R_1 + R_2 = OCH_2O$; R_3 = R_4 = OMe; R_5 = H
4: $R_1 + R_2 = R_3 + R_4 = OCH_2O$; R_5 = H



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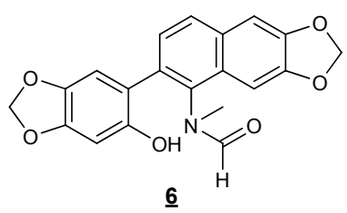

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PLANT SPECIES	PART USED	POPULAR USES	FORM OF ADMINISTRATION	REFERENCES
Z. acanthopodium DC.	Fruits	As spice. Also has been used to heal stomach ache and toothache.	Oral route (dried fruits, decoction powder).	Suryanto et al., 2004
Z. ailanthoides Siebold.&Zucc.	Bark and fruits	Epigastric pain, vomiting, diarrhea, abdominal pain, colds, snake bites.	Local and oral routes (decoction or ointment).	Sheen et al., 1994
	Tender leaves	Substitute for the green onion in Chinese dishes.	Oral route (chopped leaves)	Xiong & Shi, 1991
	Steam	Myocardium disorder attenuation, cold resistance and bone-injury alleviation.	Oral route (macerated or decoction powder).	Chou et al., 2011
Z. alatum Roxb.	Fruits, branches and thorns	Used as carminative, stomachic and as a remedy for toothache.	Local and oral routes (macerated or decoction).	Batool et al., 2010
	Seeds	Spice, aromatic tonic, stomachic and for fever, dyspepsia, cholera.	Oral route (powdered seeds, macerated powder).	
	Bark	Skin diseases, abdominal pain, anorexia, worm infestation.	Oral route (macerated or decoction powder).	
	Fruits	Mixed with salt for dyspepsia and headache.	Oral route (dry fruit).	
Z. americanum Mill.	All parts of the plant	To treat rheumatic conditions, toothaches, sore throats and burns, and as a tonic for various ailments.	Local and oral routes (macerated or decoction powder, paste, sticks).	Bafi-Yeboa et al., 2005
Z. armatum DC.	Fruits and seeds	Piscicide, aromatic tonic in fever, dyspepsia, and for expelling roundworms.	Oral route (Powder and decoction).	Ranawat et al., 2010
	Bark, branches	Carminative, stomachic and	Oral route (Infusion).	Ramanujam & Ratha, 2008

	and seeds	anthelmintic.		
Z. avicennae (Lam.) DC.	Branches and stems	Stomach tonic, to treat snake bites.	Oral route (Infusion).	Thuy et al., 1999
Z. beecheyanum K. Koch	Leaves	For treat bellyache and skin diseases.	Local and oral routes (macerated or decoction).	Cheng et al., 2004
Z. budrunga Wall.	Leaves Stem bark	Used for treating dyspepsia and some forms of diarrhea. Dysentery, coughs and headache.	Oral route (aqueous extract of the leaves) Oral route (bark juice).	Islam et al., 2001
Z. bungeanum Maxim.	Pericarps	Food condiment and seasoning in China. Treatment of vomiting, toothache, stomach ache and abdominal pain owing to roundworm.	Oral route (dried pericarps, macerated or decoction powder).	Gong et al., 2009
Z. capense (Thunb.) Harv.	Leaves	Treat fever, stomachache, flatulent colic, toothache and epilepsy.	Oral route (infusion)	Amabeoku & Kinyua, 2010
Z. caribeum Lam.	Leaves and stem bark	For asthma, spasm, fever, herpes and skin ulcers.	Oral route (macerated or decoction powder).	Schnee, 1984
Z. chalybeum Engl. *Z. chalybeum* Engl	Leaves Bark Roots	Treating severe colds and pneumonia. Malaria, colds, coughs, and dizziness. Chewed to alleviate toothaches. The Masai and Sonjo use this for small children by adding its juice to milk to give a better appetite. The decoction is given to sick goats, especially those suffering from diarrhea. Malaria, colds, coughs, toothache, sores, wounds and headache.	Local and oral routes (decoction powder, paste, sticks, juice). Local and oral routes (macerated or decoction powder, paste, sticks, juice). Local and oral routes (macerated or	Kamikawa et al., 1996 Matu & Staden, 2003 Nguta et al., 2010

	Fruits	Used in treatment of coughs.	decoction powder, paste, sticks, juice).	
Z. chiloperone var. *angustifolium* Engl.	Root bark	As antimalaric, emmenagogue and antirheumatic properties.	Oral route (decoction).	Ferreira et al., 2007
Z. davyi (I.Verd.) Waterm.	Leaves Spines Stem bark Root Root bark	To treat snakebite, severe coughs and colds and chest pains. Used for infected wounds. Treat boils, pleurisy and toothache. Used for mouth ulcers, sore throats and as aphrodisiac. Tonic both for man and animals and to treat toothache.	Local and oral routes (macerated or decoction). Local routes (infusion or decoction material, paste). Local and oral routes (macerated or decoction). Local route (Root-bark decoctions)	Tarus et al., 2006
Z. dipetalum H. Mann var. *tomentosum*	Leaves and pericap	Insecticide – ovicidal.	Local route (decoction).	Marr & Tang, 1992
Z. dugandii Standl.	Bark	Diuretic and sudorific.	Oral route (decoction).	Schnee, 1984
Z. ekmanii (URB.) ALAIN.	Leaves and roots	For malaria, in vaginal washes and to relieve toothache.	Local and oral routes (decoction).	Facundo et al., 2005
Z. fagara (L.) Sarg.	Leaves, fruits and seeds	Used as sedative and sudorific.	Oral route (decoction).	Amaro et al., 1988
Z. gillettii (Wild) Waterm.	Leaves Wood	Antihypertensive, analgesic and to treat gonorrhea. Used in house and boat-building, decorative paneling, joinery, construction of talking drums and in the paper and pulp industry.	Oral route (infusion). Wood	Addae et al., 1989 Jirovetz et al., 1999 Adesina, 2005
Z. hawaiiense Hbd.	Leaves and pericap	Insecticide – ovicidal.	Local route (decoction).	Marr & Tang, 1992
Z. hyemale A. St. Hil.	Leaves	As painkiller, sudorific, emetic and	Oral route (tea of leaves).	Guy et al., 2001

		to favor the salivation		
Z. integrifoliolum Merr.	Bark	Folk remedy for snake-bite by Ya-Mei aborigines.	Oral route (macerated or decoction powder).	Cheng et al., 2007
*Z. lemairie (*De Wild) Waterm.	Wood	House and boat-building, decorative paneling, joinery, construction of talking drums and in the paper and pulp industry.	Wood.	Adesina, 2005
Z. leprieurii Guill. et Perr.	Leaves	Used for traditional treatment of stomatitis, gingivitis, bilharzia.	Oral route (macerated or decoction powder).	Ngane et al., 2000
	Roots	As antiulcerative, antiseptic, urinary antiseptic, anti-sickler, antibacterial.	Local and oral routes (macerated powder, paste).	
	Stem barks	Used as antimicrobial, digestive aid, antidiarrheic, anticancerous, anti-odontologic and parasticide.	Local and oral routes; rectal injection (macerated or decoction powder, sticks).	Ngoumfo et al., 2010
	Fruits	Used as spices.	Oral route (dried fruits).	
	Wood	Used in house and boat-building, decorative paneling, joinery, construction of talking drums and in the paper and pulp industry.	Wood.	Adesina, 2005
Z. liebmanianum (Engler.) P. Wilson	Bark	Used to treat amebiasis, intestinal parasites, and as a local anesthetic.	Local and oral routes (decoction powder, sticks)	Navarrete, 1996 Arrieta et al., 2001
Z. limonella Alston.	Bark	Used as febrifugal, sudorific and diuretic.	Oral route (infusion, macerated powder).	Somanabandhu et al., 1992
Z. macrophylla Engl.	Bark and seeds	Used for toothache, colds, fever, malaria, stomachache, rheumatism and urogenital affections,	Local and oral routes (macerated or decoction powder, paste, sticks).	Kuete et al., 2011 Tringali et al., 2001

		as well as to prepare poisonous arrows.		
Z. monophyllum (Lam.) P. Wilson	Bark	Used as a colorant and to treat of runny nose, jaundice, ophthalmia and as an anesthetic.	Local and oral routes (macerated or decoction powder, paste, sticks).	Patiño & Cuca, 2011
Z. naranjillo Griseb.	Leaves	Preparations have been used to treat illness associated with inflammatory process.	Oral route (tea of leaves).	Bastos et al., 2001 Guy et al., 2001
Z. nitidum (Roxb.) DC	Fruits	Spice and in to treat stomachache, vomiting, diarrhea, cough, colic, and paresis and as an aromatic, stimulant and piscicide.	Oral route (dried fruits, infusion or decoction material).	Chen et al., 2011
	Root		Local and oral routes (infusion or decoction material, paste).	
Z. nitidum (Roxb.) DC	Branches, seeds and stem bark	Used in toothache, stomachache, fever, rheumatism, paresis, boils and as an insecticide and piscicide. Used in fever, diarrhea and cholera.	Oral route (infusion or decoction material).	Bhattacharya et al., 2009
Z. piperitum DC.	Pericarp	Commonly used as a spice in Japan.	Oral route (ground pericarp)	Lee & Lim, 2008
	All parts of the plant	Used to heal vomiting, diarrhea, and abdominal pain.	Oral route (macerated or decoction powder).	Yamazaki et al., 2007
Z. rhetsa Roxb.	Spines	Applied on the breast to give relief from pain and increase lactation in nursing mothers.	Local route (paste prepared by rubbing the hard spines on a rock along with water).	Lalitharani et al., 2010
	Seeds	Used as antiseptic, disinfectant, and for treat asthma, toothache and rheumatism.	Local and oral routes (seeds oil, infusion or decoction material, paste).	Reddy & Jose, 2011
Z. riedelianum Engl.		Used in different types of inflammations, rheumatism and skin stains.	Oral route (decoction)	Fernandes et al., 2009
Z. rigidum Humb. & Bonpl.	Wood	Used in building houses.	Wood	Moccelini et al., 2009

ex Willd.	Leaves	Used for toothache	Local route (ointment)	Schnee, 1984
Z. rhoifolium Lam.	Root bark	Used as a tonic, a febrifuge, against inflammatory and microbial processes, and in the treatment of malaria.	Oral route (infusion or decoction of roots bark).	Pereira et al., 2010
	Bark	Used to treat toothache and earache, also is used as an anti-venom serum, anti-tumor and in the treatment of hemorrhoids.	Oral route (decoction bark)	da Silva et al., 2007a
Z. schinifolium Sieb. & Zucc.	Leaves and ripe pericarp	Used as culinary applications and drugs for epigastric pain.	Oral route (macerated or decoction powder, crushed material).	Cao et al., 2009 Cui et al., 2009 Chang et al., 1997
Z. simulans Hance.	Roots	Used for snake bites and gastrointestinal disorders	Oral route (macerated powder).	Chen et al., 1994a Chen et al., 1994b
Z. tessmannii Engl.	Stem bark	Used for treat tumors, swellings, inflammation and gonorrhea.	Oral route (macerated or decoction powder).	Mbaze et al., 2007
	Root bark	Used as a toothbrush	Cleaning the teeth.	
	Wood	House and boat-building, joinery, decorative paneling and in the paper and pulp industry.	Wood	Adesina, 2005
Z. tetraspermum Wight and Arn.	Stem bark	Used for the treatment of dyspepsia, rheumatism and some forms of diarrhea.	Oral route (decoction).	Nissanka et al., 2001
Z. tingoassuiba A. St. Hil.	Stem bark	Antispasmodic, muscle relaxant, analgesic, sudorific, antifungal, diuretic, antiplatelet, antiparasitic and antihypertensive.	Oral route (teas or infusions).	Da Silva et al., 2008
Z. usambarense (Engl.) Kokwaro	Bark	Used to treat rheumatism.	Oral route (infusion or decoction powder).	Matu & Staden, 2003
	Young	Used as	Local route (cleaning	

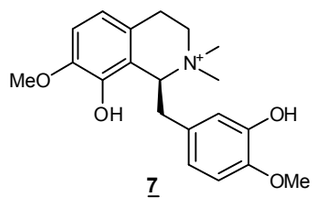
	twigs Seeds	toothbrushes. For respiratory tract infections, malaria and catarrhal fevers.	the teeth with twigs). Oral route (Grinding, hot decoction)	Nanyingi et al., 2008
Z. xanthoxyloides Waterm	Seeds Leaves and bark Leaves Roots Stem bark	Condiment in Cameroon. Used against cough, fever, colds, toothache and snake bite. As scaring and as antiseptic, astringent and laxative. Used as antiseptic, anti-sickler, digestive aid and parasticide. Also are generally used as chewing sticks for teeth cleaning. Antirheumatic, anti-odontalgic, diurectic, urinary antiseptic, digestive aid and parasticide.	Oral route (crushed seeds) Local and oral routes (infusion material, paste). Local and oral routes (macerated or decoction). Local and oral routes; rectal and vaginal injections (macerated or decoction powder, paste, sticks). Local and oral routes (macerated or decoction powder, paste, sticks).	Kassim et al., 2009 Ngassoum et al., 2003 Ngane et al., 2000

Table 1. Main ethnobotanical uses of some species of the *Zanthoxylum* genus.

Benzylisoquinoline alkaloids have a restricted distribution in plants similar to that of benzophenanthridines. In the Rutaceae family they are present in a group of five genera named proto-Rutaceae (*Phellodendron*, *Fagaropsis*, *Tetradium*, *Toddalia* and *Zanthoxylum*) (Ling et al., 2009; Waterman, 2007). In the genus *Zanthoxylum* they are not the most common but have been found in some species, such as quaternary alkaloids (*R*)-(+)- isotembetarine **7** and (*S*)-(-)-xylopinidine **8** that have been isolated from the bark of *Z. quinduense* (Patiño & Cuca, 2010).

Berberine and **protoberberine alkaloids** have been reported in several species of the genus *Zanthoxylum*, for example tetrahydroberberines such as *N*-methyltetrahydrocolumbamine **9** and *N*-methyltetrahydropalmatine **10**, have been isolated from the bark of *Z. quinduense* (Patiño & Cuca, 2010). Berberine **11** is characterized by its significant leishmanicidal and antimicrobial activities and is usually the responsible for the yellowing observed in wood and bark of some species of this genus, as in the case of *Z. monophyllum* that is used as a dye (Patiño & Cuca, 2011).

In the genus *Zanthoxylum*, **aporphine alkaloids** there are not the most representative, but they have been isolated from various species and are of great importance because several have antitumoral activity (Adesina, 2005). For example, N,N-dimethyllindicarpine **12**, obtained from the root bark of *Z. zanthoxyloides* (Queiroz et al., 2006).



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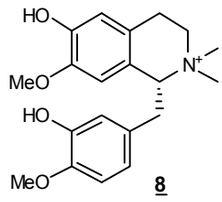

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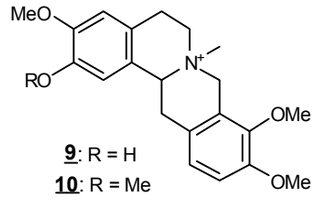
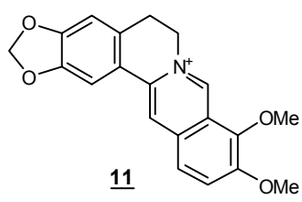


9: R = H
10: R = Me



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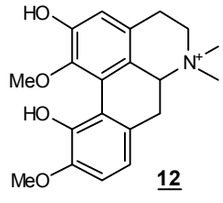

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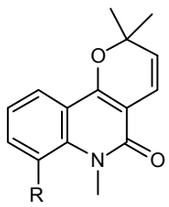
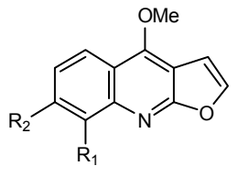
4.1.2 Quinoline alkaloids

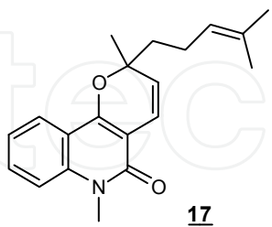
Quinoline alkaloids are very common in the genus *Zanthoxylum*, usually have been found two types: furoquinolines and pyranoquinolines. Many of them are characterized by contain a carbonyl group in position 2 of the simple quinolinic nucleus and are called 2-quinolones (Waterman & Grundon, 1983). Alkaloids of this type have been isolated from the bark of *Z. budrunga* founding two pyranoquinoline: N-methylflindersine **13** and zanthobungeanine **14**, together with two furoquinolines dictamine **15** and skimmianine **16** (Rahman et al., 2005). From *Z. simulans* also have been isolated pyranoquinoline alkaloids as zhantosimulin **17** and huajiaosimulim **18**, with cytotoxic activity (Chen et al., 1997).



13: R = H
14: R = OMe



15: $R_1 = R_2 = H$
16: $R_1 = R_2 = OMe$



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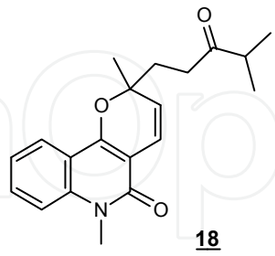
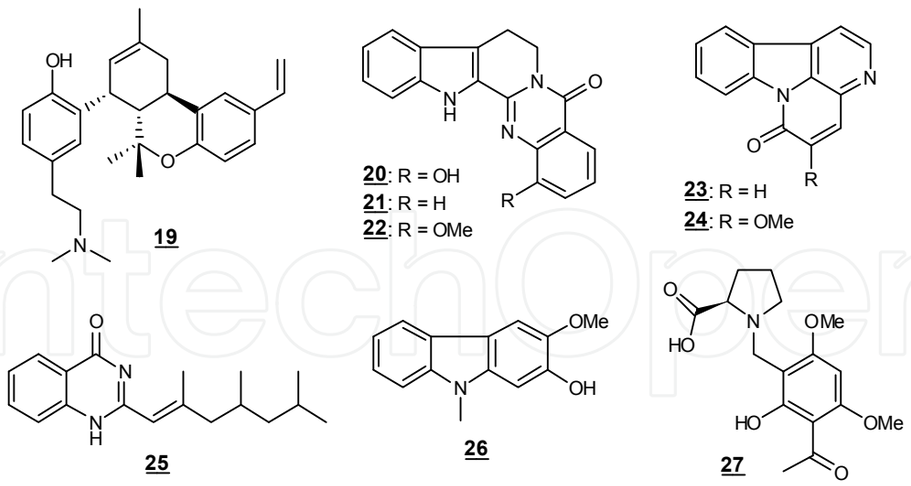


18

4.1.3 Other alkaloids

Bishoderninyl terpene, indolopyridoquinazoline, canthin-6-one, quinazoline and carbazole alkaloids, among others, are not very common in the genus *Zanthoxylum*, they have been found in some particular species. Bishoderninyl terpene alkaloids such as **19** have been isolated from the leaves of *Z. integrifoliolum* (Liu et al., 2000). Indolopyridoquinazoline alkaloids with significant antiplatelet activity as 1-hydroxyrutaecarpine **20**, rutaecarpine **21**, and 1-methoxyrutaecarpine **22** have been obtained from the fruits of *Z. integrifoliolum* (Sheen

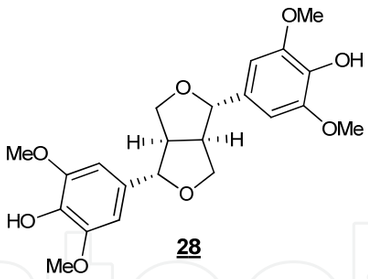


et al., 1996). Canthin-6-one alkaloids of importance for its leishmanicidal activity are rare in the family Rutaceae, are found in a few genders including *Zanthoxylum*. For example from *Z. rugosum* (Diehl et al., 2000), *Z. chiloperone* (Ferreira et al., 2002) and *Z. budrunga* (Rahman et al., 2005), have been isolated canthin-6-one **23** and 5-methoxycanthin-6-one **24**. Quinazoline alkaloids have been isolated from *Z. budrunga*, as is the case lunacridina **25** (Ahmad et al., 2003). Carbazole alkaloids such as 3-methoxy-9-methyl-9H-carbazol-2-ol **26** were obtained from the wood of *Z. rhoifolium* (Taborda & Cuca, 2007). Recently, from the bark of *Z. monophyllum* was isolated an alkaloid derived from proline, called monophyllidin **27** with antibacterial activity against *Enterococcus faecalis* (Patiño & Cuca, 2011).

4.2 Lignans

Lignans are also widely distributed in higher plants and have numerous biological activities among which include the antimicrobial, antioxidant, antitumor, antiviral, antihepatotoxic, antituberculous, insecticides and inhibit specifically certain enzymes. At the ecological level, there is the evidence that lignans play a role in plant-fungus, plant-plant and plant-insect interactions. Some lignans are toxic to fungi and insects. They are biogenetically derived by the oxidative dimerization of two C6-C3 units, that is, two characteristic phenylpropanoid units. The degree of oxidation and types of substituents determine the emerging lignan structure. There are also naturally occurring dimers that exhibit peculiar-type linkages. Different types of lignans has been described in a large number of plants from the Rutaceae family, but in the genus *Zanthoxylum* the lignans most reported have been of two types, diarylbutirolactones and 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes. Neolignans also have been reported in some species of *Zanthoxylum* (Adesina, 2005; Waterman & Grundon, 1983).

Furofuranic lignans as syringaresinol **28** were obtained from *Z. quinduense* and *Z. monophyllum* (Patiño and Cuca, 2010; 2011). From *Z integrifoliolum* (Chen et al., 1999), *Z. culantrillo* (Cuca et al., 1998) and *Z. naranjillo* (Bastos et al., 1999) ha been isolated (+)-sesamin **29**. Diarylbutirolactonic lignans such as (-)-cubebin **30** with trypanocidal activity has been isolated from *Z. monophyllum* (Cuca et al., 1998) and *Z. naranjillo* (Bastos et al., 1999). A nor-neolignan, ailanthoidol **31**, was isolated from the wood of *Z. ailanthoides*, as tree used in folk medicine in Taiwan for the treatment of snake bite and the common cold (Sheen et al., 1994).



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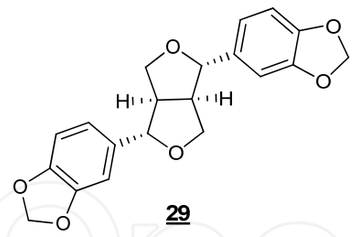

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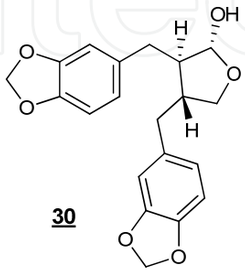

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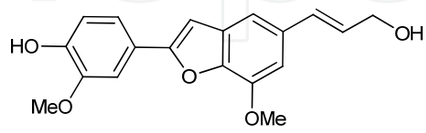
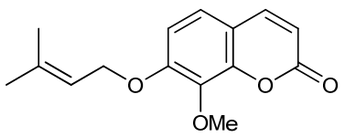


31

4.3 Coumarins

Biologically, coumarins are very useful and many of them have exhibited antibacterial, anti-tumour, vasodilatory (in coronary vessels) and anticoagulant activities. It was long noted that most coumarins are free from toxic side effects and may be given for years without side effects; overdose, however, causes haemorrhages (Murray et al., 1989). Coumarins are widespread in the Angiosperms but they are rather rare in Gymnosperms and lower plants. They are occur in great structural variety especially in the Apiaceae and Rutaceae and are additionally found in many other plants families like the Asteraceae, Poaceae and Rubiaceae (Ribeiro & Kaplan, 2002). The family Rutaceae belongs to the order Rutales characterized by the occurrence of coumarins in all families that comprise it. Coumarins, although are very frequent in the family as a whole, are confined to four sub-families (Aurantioideae, Flindersioideae, Toddalioideae and Rutoideae). In the subfamily Rutoideae is present the genus *Zanthoxylum*, which is characterized by the presence of different types of coumarins (simple, linear, dihydrofurocoumarins, furocoumarins and pyranocoumarins). The linear and angular dihydrofurocoumarins and precursors have been identified in several species of the genus, but angular dihydrofurocoumarins are not common in other species of the family Rutaceae, so it can be chemotaxonomic value for the genus *Zanthoxylum*. The fact that prenyl substitution at C-8 is much less frequent than that at C-6 could explain why angular furanocoumarins are rather rare in the Rutaceae (Murray et al., 1989; Waterman & Grundon, 1983).

From stem of *Z. shinifolium* was isolated larcinatin **32**, a terpenylcoumarin with significant inhibitory activity against the enzyme monoamine oxidase (MAO), which is one of the two isozymes, MAO-B is associated with Parkinson's disease (Jo et al., 2002). In studies done on this species, from the bark of *Z. schinifolium* were isolated auraptene **33** and collinine **34**, terpenylcoumarins with antiplatelet activity and inhibitory activity of DNA replication in hepatitis B virus (Tsai et al., 2000). Furanocoumarins with cytotoxic activity against human tumor cells have been found in berries of *Z. americanum*, for example psoralen **35** (Saquib et al., 1990).



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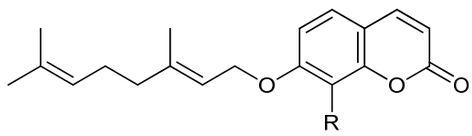
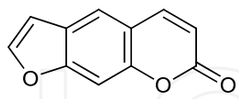


33: R = H
34: R = OMe



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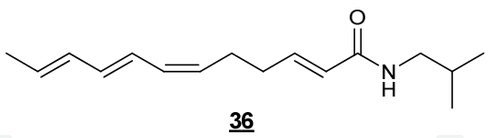
4.4 Amides

Amides are compounds that have chemotaxonomic importance for the genus *Zanthoxylum* and have been found mainly in the pericarp of the fruit, stems and roots of these species. The genus *Zanthoxylum* is characterized chemically by the frequent accumulation of olefinic alkamides (unsaturated aliphatic acid amides) and biogenetic capacity derived from the condensation of fatty acids such as linolenic and linoleic acids with isobutyl amines. Biologically, the isobutyl amides have been shown to have strong insecticidal properties. Alkamides have been used medicinally since ancient times as sialogogues, antitussive and analgesic and their presence in the *Zanthoxylum* genus may be of immense benefit to medicine (Adesina, 2005; Chaaib, 2004). An example of such amides is provided by the α-sanshool **36**, isolated from *Z. liebmannianum* and is known for its anthelmintic properties (Navarrete & Hong, 1996).

Other types of amides encountered in the *Zanthoxylum* genus are the aromatic amides described occasionally also as alkaloids or trans-cinnamoylamides. A typical example is the active antiplasmodial syncarpamide **37**, isolated from *Z. syncarpum* (Ross et al., 2004).



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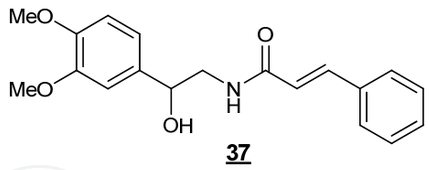
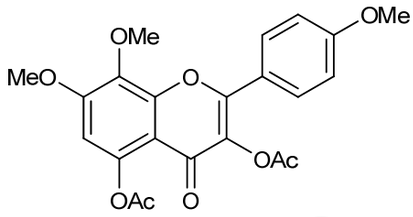


37

4.5 Flavonoids

Flavonoids are phenolic compounds widely available in this genus. They are present in almost all plant organs and play an important role in the antioxidant defense system. These secondary metabolites are known for their diverse biological properties, such as antioxidants, antiinflammatory, antithrombotic, antibacterial, antihepatotoxic, antitumor, antihypertensive, antiviral, antiallergic and estrogenic (Andersson et al. 1996; Harborne & Williams, 2000).

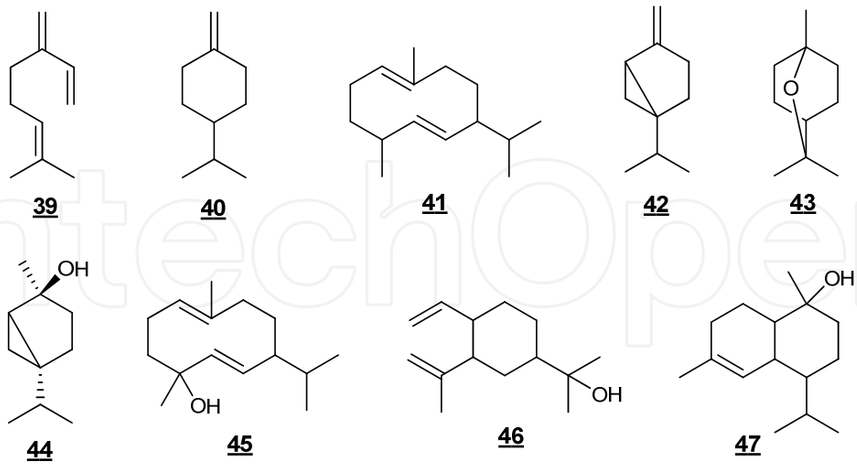
In *Zanthoxylum* genus, flavonoids are mainly represented by glycosides of flavones, flavonols and flavanones. Flavonoids found in the genus *Zanthoxylum*, like those isolated in other genera of the Rutaceae family are characterized to be polymethoxylated (Waterman & Grundon, 1983). Research carried out on fruits of *Z. integrifoliolum* lead to the isolation of 3,5-diacetyltambuline **38**, with significant antiplatelet activity (Chen et al., 1999).



38

4.6 Terpenes and sterols

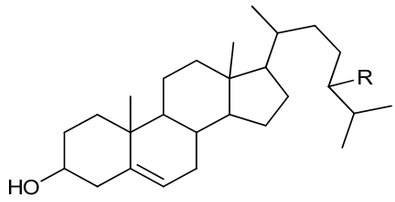
Most species belonging to the family Rutaceae contain glands that secrete volatile substances in different organs of plants such as fruits, leaves, bark, wood, roots, rhizomes and seeds. The essential oils obtained are often complex mixtures of monoterpenes and sesquiterpenes. *Zanthoxylum* genus accumulates volatile oils in leaves, flowers and fruits. Recently was determined the chemical composition of essential oils isolated from fruits of *Z. monophyllum*, *Z. rhoifolium* and *Z. fagara* by steam distillation, as well as were testing their antifungal and insecticidal activities. Gas chromatography-mass spectrometry (GC/MS) analysis allows identified 57 compounds. The main constituents in *Z. rhoifolium* oil were β-myrcene **39** (59.03%), β-phellandrene **40** (21.47%), and germacrene D **41** (9.28%), the major constituents of *Z. monophyllum* oil were sabinene **42** (25.71%), 1,8-cineole **43** (9.19%), and cis-4-thujanol **44** (9.19%), whereas fruit oil of *Z. fagara* mainly contained germacrene D-4-ol **459** (21.1%), elemol **46** (8.35%), and α-cadinol **47** (8.22%). *Z. fagara* showed the highest activity on *Colletotrichum acutatum* (EC_{50} 153.9 µL L-1 air), and *Z. monophyllum* was the most active against *Fusarium oxysporum* f. sp. *lycopersici* ($EC5_0$ 140.1 µL L-1 air). *Z. monophyllum* essential oil showed significant fumigant activity against *Sitophilus oryzae* (Prieto et al., 2011).



39 **40** **41** **42** **43**

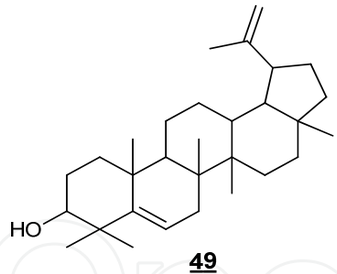
44 **45** **46** **47**

Sterols are common components of many plants and have been isolated from virtually all plants. Whereas β-sitosterol **48** appears ubiquitous in nature, the triterpene lupeol **49** appears restricted to the *Zanthoxylum* genus. Lupeol, β-sitosterol, usually associated with stigmasterol **50**, campesterol **51** and β-amyrin **52** have been isolated from the various morphological parts of the main species of *Zanthoxylum* studied (Adesina, 2005).



48: R = CH_2CH_3

50: R = CH_3



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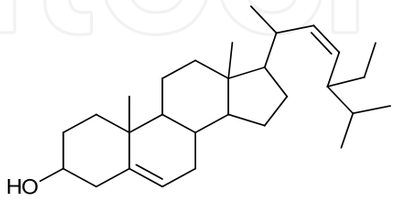

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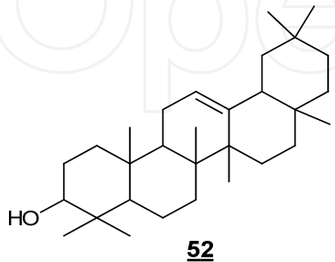

52

5. Biological activity of *Zanthoxylum* genus

As noted in previous sections, *Zanthoxylum* genus is well known for their chemical diversity and ethnobotanical properties, characteristics that have been the basis for developing various biological activity studies, which have helped to find new bioactive extracts and compounds, some of which have good potential for the development of new drugs and different industrial products.

The biological activities for certain species of the genus *Zanthoxylum* are mainly associated with the evaluation of antimicrobial, insecticidal, anti-inflammatory, antioxidant, antiparasitic, antitumor, antihelmitic, antinociceptive and antiviral activities, as well as studies of enzyme inhibition and effects on the central nervous system and cellular components of blood. The information in this section is organized by type biological activity, including the most representative results found for the genus *Zanthoxylum*.

5.1 Allelopathic activity

There are few reports on allelopathic activity of *Zanthoxylum* species. One report shows a bioguided fractionation of the ethyl acetate extract of the *Z. limonella* fruits led to the isolation of xanthoxyline, a substance with allelopathic effects of on Chinese amaranth (*Amaranthus tricolor* L.) and Barnyardgrass (*Echinochloa crus-galli* (L.) Beauv.). At a concentration of 2500 μM, xanthoxyline completely inhibited seed germination and growth of Chinese amaranth, and showed a significantly inhibitory effect on seed germination of Barnyardgrass by 43.59% (Charoenying et al., 2010).

5.2 Analgesic activity

Studies of analgesic activity in the genus *Zanthoxylum* have been focused mainly to validate its traditional uses. An example is the study of analgesic activity made with the aqueous extract of root bark of *Z. xanthozyloides*. This study showed that the extract induced analgesia, probably, by inhibiting prostaglandin production, because some isolated and

purified alkaloids of the root bark of *Z. xanthoxyloides* have anti-prostaglandin synthetase activity (Prempeh & Mensah-Attipoe, 2008).

5.3 Anticonvulsant activity

The reports on anticonvulsant activity of *Zanthoxylum* species are few. A recent study of anticonvulsant activity was carried out with the methanol and aqueous extracts from leaves of *Z. capense*. In this report was investigated the effect of both extracts on seizures induced by pentylenetetrazole, bicuculline, picrotoxin, N-methyl-DL-aspartic acid and strychnine in mice. Both extracts showed significant activity in the tests carried out with the five seizures inducing agents, finding that these substances in some cases delay seizures and in some cases act as agonists (Amabeoku & Kinyua, 2010).

5.4 Antihelmitic activity

Antihelmitic activity studies have been advanced mainly in the specie *Z. xanthoxyloides*. Two recent studies reveal that acetone: water (70:30) and ethanol extracts from leaves of *Z. xanthoxyloides* showed promising activity against *Asaris lumbricoides*, *Haemonchus contortus*, *Trichostrongylus colubriformis*, three nematodes that of these nematodes provokes production losses, clinical signs and even can lead to deaths in sheep or goats worldwide (Azando et al., 2011; Barnabas et al., 2011).

5.5 Anti-inflamatory activity

The anti-inflammatory effects of the extracts and isolated compounds of some *Zanthoxylum* species have been evaluated employed mainly four methods: 1) paw edema induced by carragenin in rats; 2) ear edema induced by phorbol myristate acetate (PMA), arachidonic acid (AA) and 12-o-tetradecanoyl-phorbol acetate (TPA) in mice; 3) inhibition of superoxide anion generation and 4) elastase release in fMLP/CB-activated human neutrophils in a concentration-dependent manner. In different studies, ethanolic extracts of bark from *Z. elephantiasis*, *Z. fagara*, *Z. martinicense* and *Z. coriaceum*, and hexane, ethyl acetate and ethanolic extracts of leaf from *Z. chiloperone* have presented promising results of anti-inflammatory activity (Villalba et al., 2007; Márquez et al., 2005; Bastos, 2001).

Other studies involving phytochemical and biological activity reported the isolation of various secondary metabolites with anti-inflammatory activity. From the hexane extract of *Z. naranjillo* was isolated a dibenzylbutirolactonic lignan (cubebin) with antiinflammatory properties (Bastos et al., 2001). In the methanol extract of stem wood from *Z. nitidum* were identified benzophenanthridine alkaloids, quinolone alkaloids, lignans and coumarins with promising anti-inflammatory activity (Chen et al., 2011). For the methanol extract of stem wood of *Z. integrifoliolum* and *Z. avicennae* have been reported the presence of phenylpropenoids, lignans, coumarins, quinolone alkaloids and quinoline alkaloids with anti-inflammatory potential (Chen et al., 2008; Chen et al., 2007).

One compound which has gained wide attention of medical professionals, pharmaceutical marketers and researchers all around the world is a dietary triterpene knows as lupeol. This compound is found in most species of the genus presented *Zanyhoxylum*, and has been

extensively studied for its inhibitory effects on inflammation under in vitro and in animal models of inflammation (Saleem, 2009).

5.6 Antimicrobial activity

Most reports of biological activity of the *Zanthoxylum* genus are related to the evaluation of antimicrobial activity. This activity has been evaluated mainly using human pathogenic strains, with few cases in which phytopathogenic strains are used. Most studies of antimicrobial activity have been made using disk diffusion method. Here are some examples of antimicrobial activity studies performed with species of the genus *Zanthoxylum*.

The antifungal and antibacterial activities of some compounds isolated from *Z. tessmannii* were determined against *Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Streptomyces viridochromogenes, Mucor miehei, Candida albicans, Chlorella vulgaris, Chlorella sorokiniana and Scenedesmus subspicatus*. 2,6-dimethoxy-1,4-benzoquinone showed activities against seven of the nine strains employed, while *3β*-acetoxy-*16β*-hydroxybetulinic acid showed weak activities against *Bacillus subtilis* and *Escherichia coli*, and *3β, 16β*-hydroxybetulinic acid showed weak activities against *Bacillus subtilis* and *Candida albicans* (Mbaze et al., 2007).

The fruits extract of *Z. armatum* has been tested for their antibacterial activity against *S. aureus*, *E. coli, Pseudomonas aeruginosa* and *Shigella boydii*. This ethanolic extract was inactive against *P. aeruginosa*, while showed positive activity on the other three strains. These results indicate that the ethanolic extract from fruits of *Z. armatum* may have broad spectrum antibacterial activity because it shows activity against *Gram*-positive and *Gram*-negative bacteria (Panthi & Chaudhary, 2006).

The essential oils of *Z. xanthoxyloides* and *Z. leprieurii*, two Cameroonian plants used as spices in local food, showed antibacterial and antifungal activity against *E. coli*, *S. aureus*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Corynebacterium glutamicum*, *B. cereus*, *B. subtilis* and *Aspergillus flavus* (Tatsadjieu et al., 2003).

Aqueous, hexane and methanol extracts of leaves, roots and stem bark obtained from *Z. chalybeum* and *Z. usambarense* were screened for in-vitro antibacterial activity using *Gram*-positive bacteria (*B. subtilis*, *Micrococcus luteus* and *S. aureus*). The root and stem-bark extracts of the two *Zanthoxylum* species showed high antibacterial activity (Matu & Staden, 2003).

Aqueous, hexane and methanol extracts of leaves, roots and stem bark obtained from *Z. chalybeum* and *Z. usambarense* were screened for in vitro antibacterial activity using *Gram*-positive bacteria (*B. subtilis*, *Micrococcus luteus* and *S. aureus*). The root and stem-bark extracts of the two *Zanthoxylum* species showed high antibacterial activity (Matu & Staden, 2003).

Ethanolic extracts of bark of *Z.fagara*, *Z. elephantiasis* and *Z.martinicense* were evaluated against *C. albicans*, *Saccharomyces cerevisiae*, *Aspergillus niger*, *A. flavus*, *Microsporum canis* and *Trichophyton mentagrophytes* to determined their antifungal activity. All of the extracts assayed showed activity against common dermatophytes of domestic animals, the one being most significant is that exhibited by the ethanolic extract of the bark of *Z. fagara* (Diéguez-Hurtado et al, 2003).

Leaf, fruit, stem, bark and root extracts of *Z. americanum* were investigated for antifungal activity with 11 strains of fungi. All extracts demonstrated a broad spectrum of antifungal activity and inhibited at least eight fungal species, being the fruit and leaf extracts the most

active in general. The results provide a basis for the very widespread use of *Z. americanum* in indigenous North American ethnomedical tradition for conditions that may be related to fungal infections (Bafi-Yeboa et al., 2005).

Chelerythrine, N-methyltetrahydrocolumbamine, N-methyltetrahydropalmatine and berberine, four alkaloids isolated from *Z. quinduense*, have exhibited promising antibacterial activity against different *Gram*-positive and *Gram*-negative bacteria, being chelerythrine the most active compound, showing an antibacterial activity comparable to that of the antibiotics kanamycine, tetracycline and anthracycline (Patiño et al., 2011).

5.7 Antinociceptive activity

In order to contribute towards the pharmacological knowledge about *Zanthoxylum* genus, as well as demonstrate the popular uses of some species as a painkiller, have been advanced antinociceptive activity studies with extracts of hexane, ethyl acetate and ethanol obtained from leaves of *Z. chilipirone* and with stem bark ethanolic extract (EtOH), its fractions of partition (hexane, ethyl acetate, aqueous) and lupeol obtained of *Z. rhoifolium*, employing animal models of chemically induced acute pain. The study carried out with *Z. chilipirone* shows that with doses of 100 and 200 mg/kg of each extract is possible to detect significantly inhibition in the paw lick, results that suggest that the extracts from *Z. chiloperone* possess constituents with antinociceptive activity (Villalba et al., 2007). Moreover, the study with extracts of *Z. rhoifolium* sought to confirm its popular use, and shows for the first time that ethanol extract of *Z. rhoifolium* stem bark, its fractions and one of the major constituents (lupeol) have antinociceptive activity when administered orally in different models of chemical nociception in mice (Pereira et al., 2010).

5.8 Antioxidant activity

To determine the antioxidant activity of substances isolated from species of *Zanthoxylum* genus have been used more than ten methods, most based on the determination of free radical scavenging activity. The most common methods are: 1) Total phenolic content; 2) DPPH radical scavenging assay; 3) ABTS radical scavenging activity and 4) superoxide anion scavenging assay.

Studies of antioxidant activity of *Zanthoxylum* species have been advanced mainly extracts from fruits and seeds. For example, the essential oil of seeds of *Z. bungeanum* (Xia et al., 2011), the ethanol extract of fruits of *Z. alatum* (Batool et al., 2010); extracts of hexane, ethyl ether, ethyl acetate and methanol obtained from fruits of *Z. piperitum* (Lee & Lim, 2008; Hisatomi et al., 2000), as well as extracts of hexane, acetone and ethanol from fruits of *Z. achanthopodium* (Suryanto et al., 2004), have demonstrated an interesting antioxidant power.

In a study made by Yamazaki and co-workers shows the isolation of two glycosylated flavonoids (hyperoside and quercitrin) of methanol extract from fruits of *Z. piperitum*, these substances scavenged DPPH radical strongly with IC_{50} values of 16 and 18 μM, respectively (Yamazaki et al., 2007).

5.9 Antiparasitary activity

In the frame of the search for new leads against the most neglegted parasitic diseases, it is of particular interest to evaluate the antimalarial, trypanocidal and antileishmanial potencial of some of the most frequently traditional drugs used.

The information on the frequently utilized antimalarial plant species is an important lead to the species that can be targeted for pharmacological, toxicological and phytochemical tests. The most important antimalarial properties have been observed in alkaloids, sesquiterpene lactones, coumarins, triterpenoids and limonoids. *Z. chalybeum*, *Z. syncarpum*, *Z. zanthoxyloides*, *Z. gilletii*, *Z. limonella*, *Z. rhoifolium* and *Z. usambarense*, among others, are some of the species of *Zanthoxylum* genus that have showed interesting antimalarial properties.

Zanthoxylum chalybeum root bark (IC_{50} of 4.2µg/ml) and some quinoline alkaloids isolated from this species have been exhibited strong antiplasmodial activity on chloroquine resistant *Plasmodioum falciparum* strain (Nguta et al., 2010). Syncarpamide and decarine, two compounds isolated from *Z. syncarpum* have showed strong in vitro antiplasmodial activity against D6 (chloroquine sensitive clone) and W2 (chloroquine resistant clone) *P. falciparum* strains, having IC_{50} values lower than 6.1 µM (Kaur *et al*., 2009; Ross et al., 2005; Ross et al., 2004). The crude alkaloid extract obtained from the bark of *Z. zanthoxyloides* and fagaronine, a benzophenanthridine alkaloid derived from the root extract of *Z. zanthoxyloides*; inhibited *P. falciparum* growth in vitro at low IC_{50} (Adebayo & Krettli, 2011; Gansane et al., 2010). Also

have been reported positive results of antimalarial activity for the ethanolic extract from stem bark of *Z. guilletti* (Zirihi et al, 2009) and for the chloroform crude extract from fruits of *Z. limonella* (Charoenying et al., 2008).

Anti-plasmodial activity of stem bark extracts from *Z. usambarense* was performed against *P. knowlesi* and *P. berghei*. The aqueous extract was remarkably active against the two parasites, while all organic solvents extracts being inactive. These results suggest that the antiplasmodial activity of *Z. usambarense* is due mainly to polar substances (Were et al., 2010).

A study of antimalarial properties of *Z. rhoifolium* bark carried out in order to validate its use and confirm the previously detected in vivo activity, lead to the isolation of antimalarial compounds. The antiplasmodial activity of *Z. rhoifolium* bark was concentrated in the alkaloid fractions showed approximately 44% inhibition of *P. falciparum* growth at 10µg/mL, using LDH micromethod. Three of the seven isolated compounds from alkaloidal fraction displayed antiplasmodial activity, ranging from good (nitidine, the most potent compound) to moderate (avicine and fagaridine) (Jullian et al., 2006). In other research of the antiplasmodial activity of *Z. rhoifolium* was determined that the water infusion from bark inhibited more than 50% the *P. falciparum* development with doses higher than 500 mg/kg (Bertani et al, 2005).

Recently, has been reported the trypanocidal effect of ethanolic extracts of leaves, fruits, stem bark and root bark, canthin-6-one alkaloids and some of its analogs obtained from *Z. chiloperone*, using *in vitro* methods and the mouse model of acute or chronic infection to evaluate the trypanocidal activity. These results demonstrate the anti-*Trypanozoma* activity of canthinones. Additionally, considering the low toxicity of canthin-6-one, is possible to propose this natural product as a possible advantageous phytotherapeutic compared to the current chemotherapy of Chagas disease (Ferreira et al., 2011; Ferreira et al., 2007). In a study carried out with the hexane extract from leaves of *Z. naranjillo* seven lignans were isolated and evaluated as trypanocidals. Four of the seven lignans showed trypanocidal activity in an *in vitro* assay, being (-)-methylpluviatolide the most active compound (Bastos et al., 1999).

Canthin-6-one alkaloids have exhibited interesting antileishmanial activity. For example, in a study carried out with the alkaloidal extract of *Z. chiloperone* stem bark reported that this extract inhibited the growth of *Leishmania braziliensis*, *L. amazonensis* and *L. donovani* at 100 μg/mL and mentioned that the compounds canthin-6-one and 5-methoxy-canthin-6-one were the two major active constituents (Ferreira et al., 2002). Also has been reported that meglumine antimonate isolated from *Z. chiloperone* showed activity against *L. amazonensis* at dose of 28 mg/kg (Sen & Chatterjee, 2011).

5.10 Antiplatelet activity

The methanolic extract of the stem of *Z. beecheyanum* showed strong antiplatelet activity in vitro using the turbidimetric method. In washed rabbit platelets, thrombin (0.1 U/mL), arachidonic acid (AA 100 M), collagen (100 g/mL), and PAF (2 ng/mL) all caused about 90-95% aggregation.

5.11 Antiviral activity

Zanthoxylum species were used in experiments to test their influence on inhibition of multiplication of porcine epidemic diarrhea virus (PEDV). The extracts of *Z. coreanum* root, *Z. planispinum* leaf and stem, *Z. schinifolium* leaf exhibited antiviral activity with the IC_{50} of 1.0, 6.4, 7.5 and 3.7 μg/mL against PEDV, respectively.

In an anti-HIV screening program, three *Zanthoxylum* species, including the root bark of *Z. ailanthoides*, the root wood of *Z. integrifoliolum*, and the stem bark of *Z. scandens* showed anti-HIV activity. The anti-HIV principles of *Z. ailanthoides* have already been proved to be two alkaloids (decarine and fagarine) and an aromatic amide ((+)-tembamide). Thus, the former two constituents, decarine and fagarine, also isolated of *Z. integrifoliolum*, can be considered as the anti-HIV constituents of the root wood of this species.

5.12 Citotoxic activity

Cancer is the leading cause of death worldwide. Finding a cure for this disease is always an important objective for human endeavor. Natural products have long been considered as potential drug candidates for cancer prevention and treatment (Chou et al., 2011). *Zanthoxylum* species are potential sources for find new antitumor agents, because diverse substances obtained from some of this species have showed strong citotoxic activity against different tumor cell lines. Following are some examples of reports about citotoxic activity of some species of *Zanthoxylum* genus.

The anti-tumor properties of the volatile oil from *Z. rhoifolium* leaves and some terpenes (α-humulene, β-caryophyllene, α-pinene and β-pinene) were investigated in vitro and in vivo using the Ehrlich ascites tumor model. Volatile oil and β-caryophyllene exhibited little direct activity against Ehrlich tumor cells in vitro, while α-humulene, α-pinene and β-pinene did not such activity. Additionally, volatile oil exhibits anti-tumor efficacy and significative immunomodulatory action *in vivo*, which may be related to β- caryophyllene associated to the synergism of other natural compounds presented in volatile oil from *Z. rhoifolium* leaves (Da Silva et al., 2007a). Other study about the citotoxic activity of essential oil from leaves of

Z. rhoifolium permitted to confirm that the essential oil is cytotoxic against tumoral cells (CD_{50} = 82.3, 90.7 and 113.6 µg/ml for A-549 (human lung carcinoma), HeLa (human cervical carcinoma) and HT-29 (human colon adenocarcinoma) cell lines, respectively), while it did not show cytotoxicity against non-tumoral cells (Vero and mice macrophages). Thus, the essential oil from *Z. rhoifolium* leaves seems to present a possible therapeuthic role due to its selective cytotoxic activity against tumoral cell lines (Da Silva et al., 2007b).

The chloroform-soluble fraction of the crude extract of leaves from *Z. ailanthoides* showed cytotoxic activity against human promyelocytic leukemia (HL-60) and myelomonocytic leukemia (WEHI-3) cells with IC_{50} values of 73.06 and 42.22 µg/mL, respectively. From this fraction were obtained four pheophorbide derivatives, where three of these compounds showed cytotoxic activities against both leukemia cells with IC_{50} value in the range of 46.76–79.43 nM (Chou et al., 2011).

The chemical investigation carried out with roots and fruits of *Z. leprieurii* led to the isolation of four acridone derivatives alkaloids were found to be moderately active against lung carcinoma cells (A549), colorectal adenocarcinoma cells (DLD-1) and normal cells (WS1) with IC50 values ranging from 27 to 77 µM (Kuete et al., 2011; Ngoumfo et al., 2010).

A chemical and citotoxic studies of the root bark of *Z. simulans* led the isolation of two citotoxic pyranoquinoline alkaloids (zanthosimuline and huajiaosimulin). These compounds were evaluated against thirteen cultured human cancer cell lines, where zanthosimuline was active against all cell lines employed, while huajiaosimulin only was active against six of the thirteen cell lines (Chen et al., 1994b).

Benzophenanthridine alkaloids are secondary metabolites commonly isolated from species of *Zanthoxylum* genus and are characterized by their potent antitumor activity, being fagaronine and nitidine the most active substances (Tillequin, 2007). Hexahydrobenzophenanthridine alkaloids are also of interest for its cytotoxic activity. Currently the alkaloid chelidonin is used in experimental oncology as the main component of Ukrain ®, an anti-cancer medicament (McManus, et al., 2007).

Berberine, an alkaloid isolated from the bark of *Z. monophyllum* showed activity against HT-29 (colorectal cancer), MCF-7 (breast cancer), HEp-2 (larynx cancer) and MKN-45 (gastric cancer) cell lines (Cordero et al., 2004). Nitidine chloride and 6-methoxy-5,6-dihydronitidine, two benzophenanthridine alkaloids isolated from *Z. macrophylla* seeds also have exhibited antitumor activity against different human cell lines (Kuete et al., 2011).

6. Conclusions

Zanthoxylum genus has proven to be a very valuable genus to the discovery and utilization of medicinal and agrochemical natural products. The collected information provides a means to understand the latest developments in the biological activity and phytochemistry of the genus. The potential for development of leads from *Zanthoxylum* continues to grow, particularly in the development of new antiparasitary, antitumor and antimicrobial agents. The information summarized here is intended to serve as a reference tool to people in all fields of ethnobothany, pharmacology and natural products chemistry.

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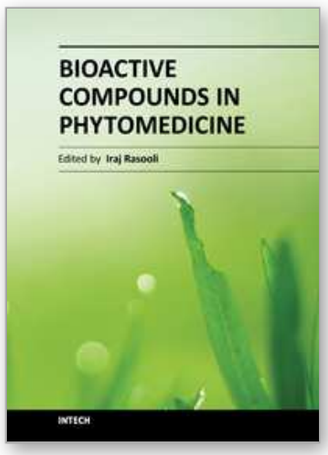

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There are significant concerns regarding the potential side effects from the chronic use of conventional drugs such as corticosteroids, especially in children. Herbal therapy is less expensive, more readily available, and increasingly becoming common practice all over the world. Such practices have both their benefits and risks. However, herbal self-therapy might have serious health consequences due to incorrect self-diagnosis, inappropriate choice of herbal remedy or adulterated herbal product. In addition, absence of clinical trials and other traditional safety mechanisms before medicines are introduced to the wider market results in questionable safe dosage ranges which may produce adverse and unexpected outcomes. Therefore, the use of herbal remedies requires sufficient knowledge about the efficacy, safety and proper use of such products. Hence, it is necessary to have baseline data regarding the use of herbal remedies and to educate future health professionals about various aspects of herbal remedies.

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