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Chemistry and pharmacology of some plants mentioned in the letter of Pero Vaz de Caminha

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ABSTRACT

Brazil has a long tradition in the study of medicinal plants. When the Portuguese arrived to the new colony, Pero Vaz de Caminha, the scriber of the fleet, left the first impressions of the local and the inhabitants. He clearly mentions how the Indians use natural dye as tincture to paint their bodies. This article reviews the phytochemical and pharmacological characteristics of these colorants and other medicinal plants recently identified mentioned in this letter.

Keywords: *Ethnobotany - Historical ethnobiology – Medicinal plants - Natural products*

INTRODUCTION

The first description of Brazilian natural richness is the letter Pero Vaz de Caminha, sent to D. Manoel, king of Portugal, soon after the arrival of Cabral in 1500. The letter is considered Brazil's birth certificate. Talking about the appearance of the original inhabitants, Caminha, the scriber of the expedition, penned: 'They go about naked, without clothing. They do not bother about to cover or to uncover their bodies, and show their private parts as readily as they show their faces. In this matter they are of great innocence. Walking among them there were three or four women, young and gentle, with their hair very black and very long, loose to their backs; their private parts, so prominent and so neat, and so clean of their hairs that we, by very much looking at them, did not get ashamed (...) and sure she was so good shaped and so rounded, and her private part so graceful that most women in our land, if had seen those features would feel abashed for not having their own like she has hers" (Caminha [1500], 2013).

In some parts of his letter Caminha also described the reddish and black color of their bodies. "They are brown skinned, of a quite reddish complexion, with handsome faces and noses, in such "scarved" features. There was one man there, who spoke much to the others, telling them to go away, but they did not, in my opinion, they respected or feared him. This one who was telling them to move carried his bow and arrows, and was painted with red paint on his breasts and shoulder blades and hips, thighs, and legs, all the way down, and the unpainted places such as the stomach and belly were of their own color, and the paint was so red that the water did not wash away or remove it, but rather when he came out of the water he was redder (...). Some of them

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were carrying prickly green nut shells from trees, which in color resembled chestnuts, except that they were very much smaller. And these were full of small red grains which, when crushed between the fingers, made a very red paint with which they were painted. And the wetter they got, the redder they became. They are all shaved above the ears, as well as their eyebrows and eyelashes. All of them have their foreheads from temple to temple painted with a black paint, which looks like a black ribbon the breadth of two fingers" (Caminha [1500] 2013).

The red color came from bixin (**1**, Figure 1), the pigment from the seeds of urucum, *Bixa orellana* L. while the black dye, genipin (**2**, Figure 2), came from *Genipa americana* L.

As a matter of fact, Caminha never mentioned a plant as being medicinal. The Portuguese stayed here for less than two weeks. All he says is 'rice', 'fruits', 'seeds', 'palms', 'yam'. However, Andrade-lima (1984) and Filgueiras and Peixoto (2002) suggested that the basket the Indians carried the seed of urucum could be fruits of *Lagenaria vulgaris* L. These authors also identified, from species levels, some plants mentioned in Caminha's letter: *Euterpe americana* Mart., *Astrocaryum ayri* Mart., *Attalea funifera* Mart., *Halodule wrightii* Asch., *H. emarginata* Hartog, *Gynerium sagitatum* (Aubl.) P.Beauv., *Bixa orellana* L., *Protium heptaphyllum* (Aubl.) Marchand, *Genipa americana* L. and *Lagenaria siceraria* (Molina) Standl. Phytochemical and pharmacological analysis has been made with the last four. The use of urucum and genipin, either in medicine or as body tincture, was mentioned by Gabriel Soares de Sousa, Fernão Cardim, Piso, Langsdrorff, Freire Allemão, Hans Staden and other naturalists or travelers (Alves 2010, 2013).

In this paper, we will discuss the chemistry and pharmacology of these two colorants and other medicinal plants mentioned in the letter of Pero Vaz de Caminha

Bixa orellana L.

Native to Central and South America, urucum, also known as açafrão, açafroa, annatto, urucu, has been used in traditional medicine for many ailments (Mors et al. 2000; Lorenzi and Matos 2008). It is a bushy shrub with a height ranging from 3 to 10 meters. Bark is more or less smooth with many warty lenticels. Leaves are ovate with a round, heart-shaped base and a pointed tip. The flowers are white, pink, or purple colored (Venugopalan et al. 2011). Its use has been traced to the 15th and 16th centuries when tribes of Central and South America employed it extract as body painting to rid them from evil spirits well as an insect repellent (Venugopalan et al. 2011).

Bixin, is an apocarotenoid and the first *cis*-poliene of natural origin. Along with norbixin it is the main component of urucum. Other apocarotenoids, rather than bixin, have been isolated by Jondiko and Pattenden (1989) and Mercadante et al. (1996, 1997, 1999).

A pentacyclic triterpene named tomentosic (**3,** Figure 1) acid was isolated from its root (Schneider et al. 1965) and a tetracyclic sequiterpene, ishwarane, along with a series essential oils were obtained by Lawrence and Hogg (1973). Galindo-Cuspinera et al. (2002) detected 107 compounds, of several classes (alcohols, aldehydes, alkanes, alkenes, ketones, and terpenes) 51 of which were positively identified. The presence of free fatty acids, alcohols, aldehydes, ketones, sulphur compounds, furans, esters, hydrocarbons, monoterpenes, diterpenes and sesquiterpeness was isolated by Giorgi et al. (2013).

From the fatty soluble antioxidant fraction Frega et al. (1998) reported the isolation of tocotrienols, mainly α-tocotrienol. Monzote et al. (2013) identified 73 essential oils from its seeds, of which ishwarane (**4**, Figure 1) and geranylgeraniol (**5**, Figure 1) were the major components (18.6% and 9.1%, respectively).

Its roots are used as digestive and diuretic, fresh shoots steeped in water as an eye wash for inflamed eyes, leaf decoction to lessen vomiting during pregnancy. The seed paste is indicated as an aphrodisiac and as protection against insect stings and in syrup against pharyngitis and bronchitis. The seeds are also recommended in cases of intestinal catarrh, measles and as an emmenagogue (Lorenzi and Matos 2008; Mors et al. 2000).

In his *História Natural e Médica das Índias Ocidentais,* Piso ([1648], 1954) observed that the grains of this plant, when new, ripe and dry, and reduced to tablets are mixture with the pulp *Tipioca* are useful in envenomation or to any other illness. It is an exaggeration, of course. However, its use as anti-inflammatory, analgesic, as radical scavengers,

antidiarrheal, anticonvulsant, in the treatment of gastric ulcers, antibacterial against *Escherichia coli, Staphylococcus aureus,* and *Shigella dysenteriae* has been recorded (Shilpi et al. 2006).

The ethanolic extract of its seeds and leaves showed activity against Gran positive and Gran negative bacteria like *Bacillus subtilis, Streptococcus pyogens, Salmonella typhi, Pseudomonas aeruginosa,* and the yeast like fungus *Candida albicans* (Fleischer et al. 2003; Venugopalan and Giridhar 2012). Stem's, leaves' and root's extracts showed activity against *Bacillus cereus, S. aureus, Salmonella tiphinurium, P. aeruginosa, Pseudomonas mirabilis* and *Mycobacterium tuberculosis* (Silva et al. 2010). The same extract also showed activity against *Bacillus pumilus* (Castello et al. 2002). Antimicrobial activity against *Kleibsiella pneumoniae, Enterococcus fecalis, Vibrio cholera, Moracella catharrhalis* along with fungal pathogens *Aspergillus niger* and the dermatophytes *Trichophyton mentagrophytes* and *T. rubrum* have also been observed (Tamil Selvi et al. 2011). A preliminary data from the volatile components of annatto as insect (*Aedes aegypt*) repellent was detected by Giorgi et al. (2013) corroborating its use by the Indians.

In an experiment to verify the neutralization of the hemorrhagic effect of the venom of *Bothrops atrox*, Otero et al (2000a,b,c) tested 75 extracts of plants used in traditional medicine for snake bites. The results demonstrated that 31 extracts (41.3%) had in vitro moderate or high neutralizing ability against the hemorrhagic effect of the venom and that *Bixa orellana* (with other 11 species) was 100% effective. Later, the same group determined the neutralizing activity of 12 ethanolic extracts against the edema-forming, defribrinating and coagulant effects of *B. asper* venom. According to the authors, all extracts were partially effective in a dose-dependent manner, with *B. orellana*, and three other species, showing the highest effect (Nuñes et al. 2004).

The hypolipidemic property of its seeds (Ferreira et al. 2013), the diuretic activity of its leaves (Radhinka et al. 2010), its anticonvulsant action (Patnaik et al. 2011), its antitumor effect (Matuo et al. 2013; Pierpaoli et al. 2013) and its antigenotoxic, antimutagenic and clastogenic potential (Antunes et al. 2005; Junior et al. 2005) have also been demonstrated.

Annatto also lowers blood glucose in dogs (Russell et al. 2005, 2008) and mice (Patnaik et al. 2011). It also lowers the levels of LDL (low density lipoprotein, the 'bad cholesterol') and total cholesterol, and, at the same time, it raised that of HDL (high density cholesterol, the 'good cholesterol'), then suggesting a hypocholesterolomic effect (Paula et al. 2009).

It has also been demonstrate that *Bixa orellana* can also surpass the adverse effects of some drugs. For example, isoprenalin (or isoproterenol) is a potent, non-selective adrenergic agonist receptor used in emergencies to stimulate heart rate in patients with bradycardia or heart block. However, its adverse effects may include palpitation, tachycardia, cardiac ischemia and arrhythmias (Goodman and Gilman 1996).

Pretreatment with the ethanolic extract of annatto offered protection against isoproterenol-induced myocardial injury in rats (Asokkumar et al. 2012).

Bixin itself and its derivatives exert protective effects against retinal degeneration induced by tunicamycin both *in vivo* and *vitro,* by inhibiting an early apoptotic event and following caspase-3 activation (Tsuruma et al. 2012). Its antioxidant properties are associated with its ability to scavenge free radicals, which, in turn, reduce damage and protect tissues against toxicity caused by antitumoral drugs such as cisplatin (Rios et al. 2009; Santos et al. 2012).

Geranylgeraniol, one of the main component of the oil isolated from its seeds showed activity against the intracellular amastigote form of *Leishmania amazonensis* (Lopes et al. 2012; Monzote et al. 2013), while ishwarane exhibited moderate antifungal activity against *Candida albicans,* low activity against *Tricophyton metagrophytes*, and low antibacterial activity against *E. coli, S. aureus* and *P. aeruginosa*, but was inactive against *B. subtilis* and *A. niger* (Raga et al. 2011).

The anti-inflammatory property of urucum is associated, at least in part, with its antibradykinin activity, reduction of NO production and inhibition of vascular endothelial growth factor (VEGF) (Yong et al. 2011, 2013a,b). As regards to these antibacterial properties mentioned above, annatto can also be used as colorant in food industry. It is safe, without

mutagenic, carcinogenic or toxic side effect (Agner et al. 2004; Bautista et al. 2004; Alves de Lima et al. 2003; Karchuli and Ganesh 2009; Paumgarten et al. 2002; Viuda-Martos et al. 2012). Annatto is also important in cosmetic industries especially lipstick then its nickname of 'lipstick industries' (Venugopalan et al. 2011).

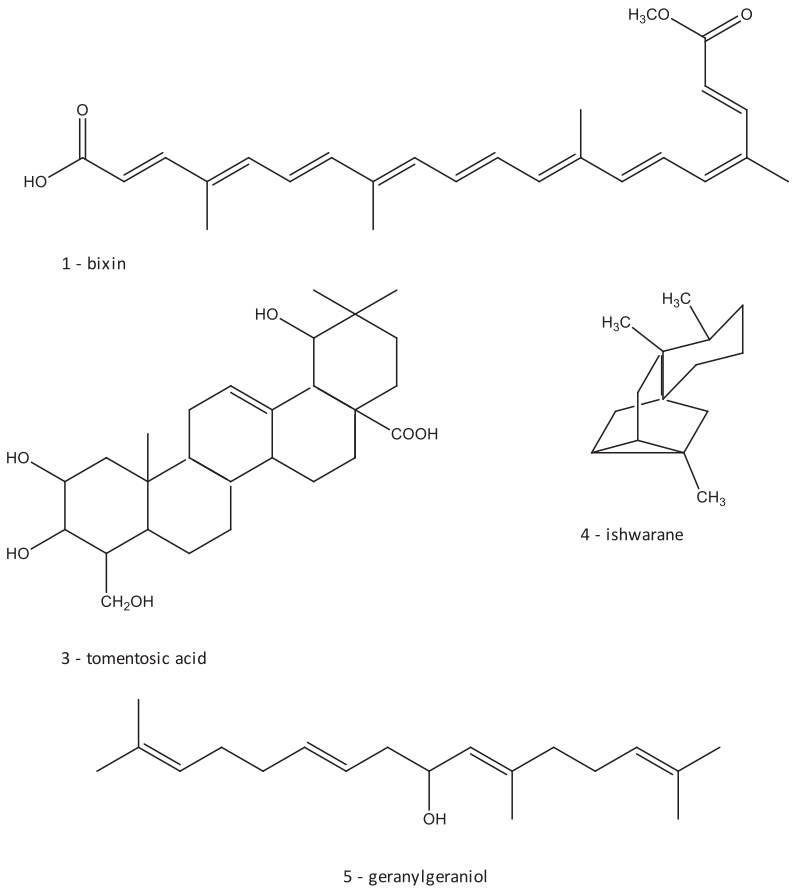

Figure 1. Structures of bixin (1), tomentosic acid (3), ishwarane (4), geranylgeraniol (5).

Genipa americana L.

The mention of genipin is as older as that of bixin. Gabriel Soares de Sousa, Fernão Cardim ([1585], 1997), Hans Staden ([1557], 1988) and Wilen Piso ([1648], 1954) described, with almost the same words, its use as body tincture. They observed that, when isolated from the fruits, the ink is blank. However, after some after application it acquired a black colour well appreciated by the Indians. Sousa, Cardim and Piso attributed wound healing properties to the fruit of this plant (Alves 2010, 2013). Piso ([1648], 1954) also suggested that this black colour serves to frighten the enemies.

The structure of genipin was established in 1961 by Djerassi et al., almost five centuries after the first descriptions made by earlier naturalists. It is the aglycone of geniposide (Guarnaccia et al. 1972). Genipin and/or geniposide can also be found in *Randia spinosa* (Hamerski et al. 2003), *Eucommia ulmoides* (Hirata et al. 2011; Nam et al. 2013; Zhang et al. 2013), *Castilleja tenuiflora* (Carrilo-Ocampo et al. 2013) and *Bellardia trixago* (Venditti et al. 2013). Geniposide is hydrolyzed to the aglycone genipin by bacterial enzymes in the intestines and the liver (Jeon et al. 2011).

Their pharmacological and phytochemical properties have been studied by several authors. In 1991, Ueda et al. reported the isolation of iridoid glycosides geniposide (**6**, Figure 2) and geniposidic acid (**7**, Figure 2) from the fruits and of

geniposidic acid from the leaves of jenipapo. On callus induction, the plant produces geniposidic acid and gardenoside (**8**, Figure 2) in high levels. These iridoids show anti-tumor activities. Some fifteen year later, Ono et al (2005, 2007) found four new iridoid glycosides: genameside A-D (**9-12**, Figure 2) and still later, three new monoterpenoids: genipacetal (**13**, Figure 2), genipamide (**14**, Figure 2), and genipaol (**15**, Figure 2). No therapeutic activity was attributed either to glycosides or to terpenoids. On the other hand, Conceição et al. (2011) isolated only steroids which showed a significant anticancer effect associated to inhibition and reactivation to ERKI/2 and p38 in Be Wo cells.

Studies of genipin and geniposide isolated from the fruits of *Gardenia jasminoides* Ellis have shown that either the latter or the former can be useful in the treatment of allergic asthma (Deng et al. 2013), ophthalmic disease (Koriyama et al. 2013; Song et al. 2013), antiviral (Lin et al. 2013), cardiovascular disorders (Hwa et al. 2011; Jiang et al. 2013; Zhang et al. 2013), vitiligo (Jun et al. 2008), angle sprain (Chen et al. 2009), antidepressant (Tian et al. 2010), traumatic brain injury (Hughes et al. 2014), Alzheimer (Gao et al. 2014; Nam and Lee 2013), in diabetes (Guan et al. 2013; Guo et al. 2012; Liu et al. 2012, 2013a,b; Ma et al. 2013; Qiu et al. 2012), in inflammation (Fu et al 2012; Khanal et al. 2014; Li et al. 2012; Wang et al. 2012; Zhang et al. 2012), hepatic ischemia (Kim et al. 2013) and cancer (Ayyasamy et al. 2011; Dando et al. 2013; Khanal et al. 2012; Kim et al. 2012; Wang et al. 2012; Yang et al. 2013).

In many cases, the mechanisms of action underlying genipin and geniposide properties have been established. For example, intraperitoneal treatment with geniposide prevents eosophinolic pulmonary infiltration, attenuates the increases of interleukins IL-4, IL-5 and IL-13, making it an effective adjuvant for the treatment of allergic asthma (Deng et al. 2013).

Genipin suppresses of UCP-2 (uncoupling protein 2), a mitochondrial carrier protein involved in the negative regulation of insulin secretion (Zhang et al. 2006). Over expression of UCP2 is also involved in many types of cancer. It also regulates the activation of proapoptotic proteins and improves insulin sensitivity by promoting insulin-stimulated glucose consumption and glycogen synthesis. In addition, genipin, in a dose and time dependent way increases the expression of peroxisome proliferator-activated receptor, which, in turn, inhibits vascular cell adhesion molecule-1, a protein that mediates the cell adhesion of lymphocytes, monocytes, eosinophils and basophils to vascular endothelium, and may play a role in the development of atherosclerosis. Genipin down-regulates the production of pro-inflammatory cytokines (TNF-β, IL-1, IL-6), reduces the activation of NF-kβ (nuclear factor-beta), a protein complex linked to cancer, inflammatory and autoimmune diseases, and inhibits the expression of COX-2, an enzyme involved in the inflammatory process. Moreover, genipin induces the expression and activity of HO-1, an inducible isomer of heme oxygenase (HO), a microsomal enzyme that contributes to the anti-inflammatory of cells and tissues.

These results make the use of genipin a good candidate against diabetes and cancer. (Ayyasamy et al. 2011; Dando et al. 2013; Guan et al. 2013; Hwa et al. 2011; Jeon et al. 2011; Jiang et al. 2013; Khanal et al. 2012; Kim et al. 2012; 2013; Li et al. 2012; Qiu et al. 2012; Liu et al. 2013; Wang et al. 2012; Wang J et al. 2012; Wang N 2012; Yang et al. 2013).

Geniposide shows similar actions. It blocked the production of TNF-α, IL-6 and IL-1β potentiates the expression of HO-1, increases insulin secretion through-like peptide receptors, prevents or improves the impairment of insulin secretion in b cells challenged with high concentration of glucose, decreases the level of Ab 1-42, a major component of amyloid plaques that accumulates in neurons of Alzheimer's disease. Like genipin, geniposide significantly inhibits platelet aggregation induced by thrombin/collagen and venous thrombosis induced by tight ligation of the inferior vena cava (Fu et al. 2012; Guo et al. 2012; Kim et al. 2012; Liu et al. 2012; Liu et al. 2013a,b; Wang J et al. 2012; Wang N 2012; Zhang et al. 2013a,b).

Thus, geniposide may be an efficient drug in the treatment of inflammation, diabetes, Alzheimer's and thrombotic diseases. Geniposide also exerts protective effects against hepatic steatosis, a process which describes the abnormal retention of lipid (Ma et al. 2011). It was also demonstrated that the lethal dose of geniposide was 1431.1 mg/kg (Ding et al. 2013).

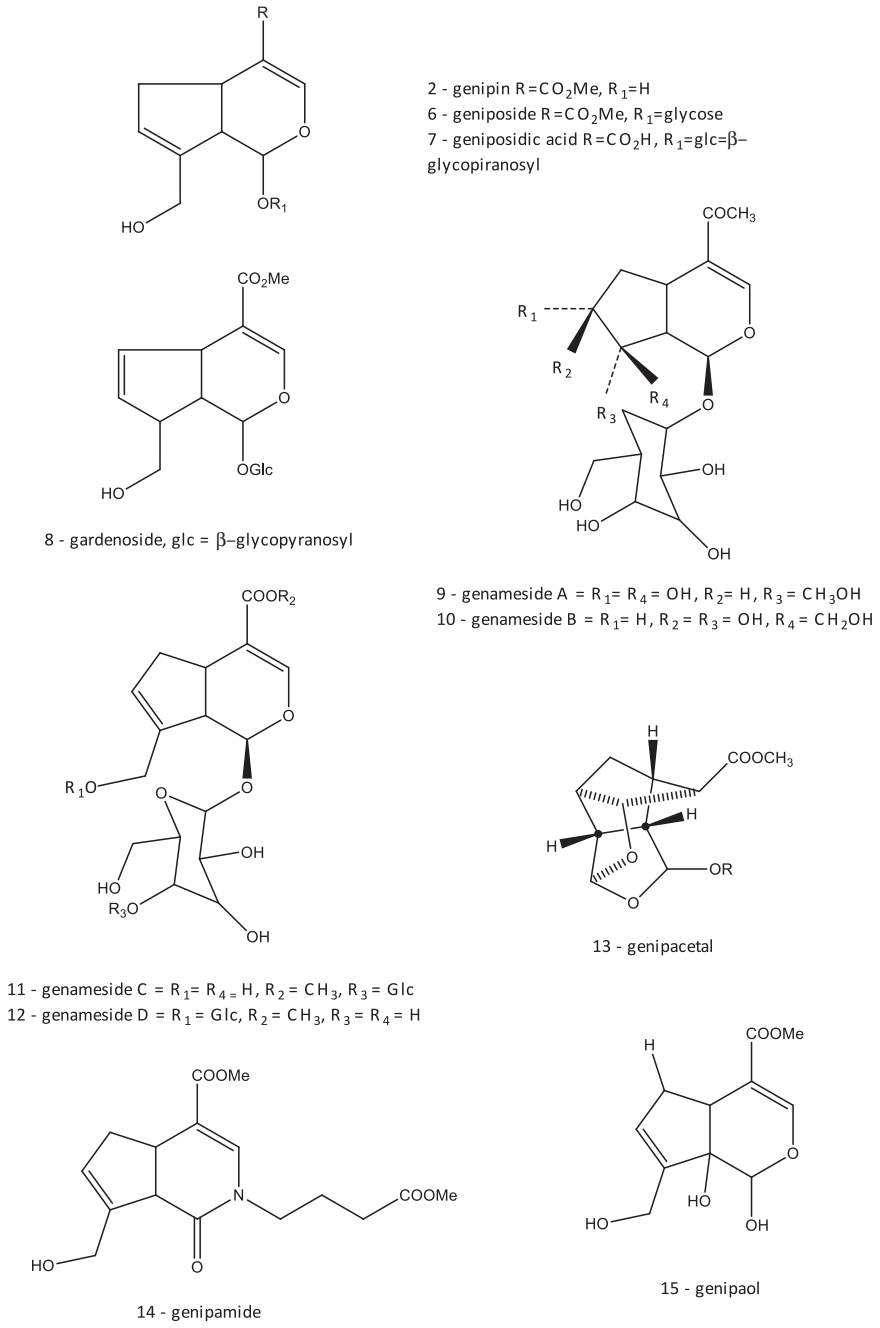

Figure 2. Structures of genipin (2), geniposide (6), geniposidic acid (7), gardenoside (8), genameside A-D (9-12), genipacetal (13), genipamide (14), genipaol (15).

Protium heptaphyllum (Aubl.) Marchand

P. heptaphyllum, also known as almecega, breu-branco, elemi, icicariba is largely found in North and Northeast Brazil and traditionally used for many ailments (Mors et al. 2000; Lorenzi and Matos 2008). The plant, with its medicinal use, was described by Gabriel Soares de Sousa, Fernão Cardim, Wilen Piso and Luis Gomes Ferreira, naturalists who visited Brazil in the colonial time (Alves 2010, 2013).

Its resin is rich in pentacyclic triterpenes like α– and β-amyrins (**16-17**, Figure 3) (Susunaga et al. 2001) which are responsible for their therapeutic

actions, analgesic (Aragão et al. 2007; Chicca et al. 2012; Otuki et al. 2005; Silva et al. 2011), anti-inflammatory (Aragão et al. 2007; Oliveira et al. 2004a; Siani et al. 1999; Silva et al. 2011), periodontitis (Pinto et al. 2008), colitis (Matos et al. 2013; Vitor et al. 2009), pancreatitis (Melo et al. 2010, 2011), hepatoprotective (Oliveira et al. 2005), gastroprotective (Araújo et al. 2011; Oliveira el al. 2004a,b,c;), antihyperglycemic (Santos et al. 2012), antihyperglycemic (Santos et al. 2012), anxiolytic and antidepressant (Aragão et al. 2006) and antipruritic (Oliveira et al. 2004a). Its esters and acetate also possess anticancer (Barros et al. 2011), antimicrobial (Diaz-Ruiz et al. 2012) antihyperglycemic activities (Singh et al. 2009).

The mechanisms of action responsible for its anti-inflammatory and antinociceptive (which are often associated) have been discussed for several authors. Usually, it has been attributed to the increasing COX-2 and EGF expression (Araújo et al. 2011; Silva et al. 2011; Vitor et al. 2009). Its visceral nociception involves the opioid and vaniloid mechanism (Lima-Junior et al. 2005).

The inhibition of protein kinase-A and protein kinase-C was suggested by Otuki et al. (2005) and Chicca et al. (2012), respectively. Another possible mechanism for the activity of amyrins is that of cannabinoid receptors (Chicca et al. 2012; Matos et al. 2013; Silva et al. 2011).

In pancreatitis, they greatly suppressed inflammatory cell infiltration, acinar cell necrosis, the expression of TNF-α and the inducible nitric oxide synthase, decreases the serum levels of amylase and lipase and of interleukin IL-6 and the activity of pancreatic mieloperoxidase (MPO) (Melo et al. 2010, 2011).

Both α– and β-amyrin attenuates acute periodontal inflammation by reducing neutrophils infiltration, oxidative stress, the production of the pro-inflammatory cytokine TNF-α and the inhibition of gingival MPO (Pinto et al. 2008), while the sedative effect of these two pentacyclic triterpenes involves benzodiapene-type receptors (Aragão et al. 2006) while its antipruritic action may be related to a stabilizing effect on mast cell membrane (Oliveira et al. 2004a).

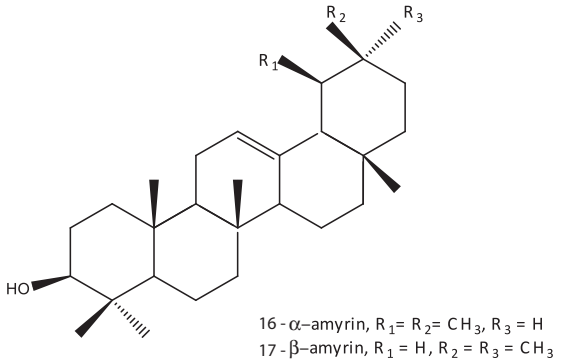

Figure 3. Structures of amyrin (16), amyrin (17).

Lagenaria siceraria (Molina) Standl.

Known as calabash, opo squash, bottle gourd and long melon in English and as cabaça cuia, cuieté, jamaru, porongo and taquera in Brazil, was one of the first cultivated plant in the world, grown not primarily for food, but for use as a water container. It may have been carried from Africa to Asia, Europe and the Americas in the course of human migration or by seeds floating across the oceans inside the gourd. It has been proven to be in New World prior to the arrival of Columbus. Although indigenous to Africa this species reached America from Asia by 10,000 years before present (B.P.) and had a broad New World distribution by 8,000 B.P. (Erickson et al. 2005).

It contains pentacyclic triterpenes, sterols, flavonoid glycosides and polysaccharides which may be responsible for its therapeutic properties (Chen et al. 2009; Ghosh et al. 2008, 2009).

From the methanolic extracts of its fruits Gangwal et al (2010), isolated oleanolic acid, sitosterol, campesterol, isoquercitrin and kaempferol, while Chen et al. (2008), reported the isolation, identification and structural elucidation of nine (four new and five known) D:C friedooleanane type triterpenes from its stem (**18-26**, Figure 4). One of the new (**20**) and one of known (**26**) showed significant anticancer activity against the SK-Hep 1 cell lines.

Preliminary studies show that its leaves and/or fruits may be used as analgesic (Shah and Seth 2010), anti-allergic (Jasani et al. 2012), anti-asthmatic

(Jasani et al. 2012), anticancer (Killedar et al. 2012; Saha et al. 2011; Sen et al. 2013), antidepressant (Prajapati et al. 2011), antihyperlipidemic (Ghule et al. 2006a,b, 2009), antimicrobial (Rodge and Biradar 2012), antioxidant (Deshpande et al. 2007; Erasto et al. 2009; Mayakrishnan et al., 2012, Sharma et al. 2013), cardioprotective (Fard et al. 2008; Saha et al. 2011; Upaganlawar and Balaraman 2011), anti-diabetes (Teugwa et al. 2013), hepatoprotective (Lakshmi et al. 2011), in obsessive compulsive disorder (Prajapati et al. 2011) and in urolithiasis (Takawale et al. 2012).

Phytochemical and pharmacological reviews have been described (Aslam and Najam 2013; Deshpande et al. 2008; Gorasiya et al. 2011; Kubde et al. 2010; Kumar et al. 2012; Tyagi et al. 2012). However, for the most part, the bioactive principles responsible for such activities remain to be elucidated.

Tests with different extracts show different results. The analgesic property of methanolic and aqueous extracts of its fruits was evaluated. The former showed a moderate activity, while the latter showed a significant one (Shah and Seth 2010).

Hyperlidemia, a pathology characterized by an increased level of total cholesterol, triglycerides and low-density protein along with a decrease in high-density lipoprotein cholesterol, is closely associated with the development of atherosclerosis. Ghule et al. (2006a,b, 2009) tested the hypolipidemic effect of oral administration of four different extracts, aqueous, methanolic, petroleum ether and chloroform, from *Lagenaria siceraria* fruits in experimental hyperlipidemic induced rats. Both chloroform and alcoholic extracts exhibited more significant effects in lowering total cholesterol, triglycerides, and low density lipoprotein along with increase in HDL as compared with the others, while petroleum ether extracted did not show significant activity. The results show a dose-dependent inhibition of total in the levels of cholesterol, triglycerides and low-density lipoprotein and a significant increase in that of high density lipoprotein, giving a scientific basis for the use of bottle gourd in coronary diseases.

Kalsait et al. (2011) reported the isolation of four phytosterols, fucosterol, racemosol, stigmasterol and one stigmasterol derivate with a significant activity in lipid profile. The levels of cholesterol, triglycerides, LDL and VLDL (very low density lipoprotein) were reduced while that of HDL cholesterol increased. These results corroborate the use of *L. siceraria* in the treatment of hyperlidemia.

Another example of the influence of extracts was provided by Rodge and Biradar (2012). The acetone, methanol and distilled water of extracts of leaves exhibited a significant microbial activity against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis* and *Candida albicans.* Again, petroleum ether showed the least activity.

Pretreatment with *Lagenaria siceraria* fruits during 51 days protects the heart of rats against cardiotoxicity produced by isoprenalin (Mali and Bodhankar 2010, Upaganlawar and Balaraman 2011), in a similar way of that discussed above for *Bixa orellana.* Another example is provided by doxorubicin, an anthracycline antibiotic widely used in the chemotherapy of breast cancer. However, its acute administration induces cardiotoxicity manifested by a significant increase in serum creatine-kinase MB isoenzyme and lactate desidrogenase.It also increase lipid peroxidation and free radical formation. Both hydroalcoholic seed and fruit powder extracts of this plant show protective effect against cardiotoxicity induced by doxorubicin (Fard et al. 2008; Singh et al. 2012).

Evaluation of antitumoral activities of aerial parts and fruits of *Lagenaria siceraria* have been reported. The active principle, however, remains undetermined (Killedar et al. 2012; Saha et al. 2011; Sen et al. 2013). At the same time, Ghosh et al (2008, 2009) reported the isolation and identification of a polysaccharide from the stem of the plant with cytotoxic property against adenocarcinoma cell line (MCF-7).

Ribosome-inactivating proteins are a class of proteins as a putative role in plant's defense against pathogens. They can also act as antitumor, immunosuppressive, antiviral and anti-HIV. Lagenin, an ribosome-inactivating protein was isolated from the seeds of *Lagenaria siceraria* by Wang and Ng (2000), corroborating the antitumoral use of this plant.

Bottle gourd fruit extract also protect against hepatotoxicity induced by carbontetrachloride. This protective action is presumably due to its chemical components which prevents the

accumulation of free radicals and to detoxification mediated by glutathione (Lakshmi et al. 2011).

Although important to any metabolic process, the excessive generation of free radicals is involved in the development of several ailments, such as diabetes, cancer, arteriosclerosis, cardiovascular diseases, arthritis, among others. Natural antioxidants react with free radicals acting as oxygen scavengers, thus protecting cells form cellular damages induced by oxidative stress (Sharma et al. 2013). The antioxidant and free radical potential of *Lagenaria siceraria* fruits and seeds has been described by several authors (Deshpande at al. 2007; Erasto and Mbwambo 2009; Mayakhrisnan et al. 2012; Mohan et al. 2012; Sharma et al. 2013; Sulaiman et al. 2013).

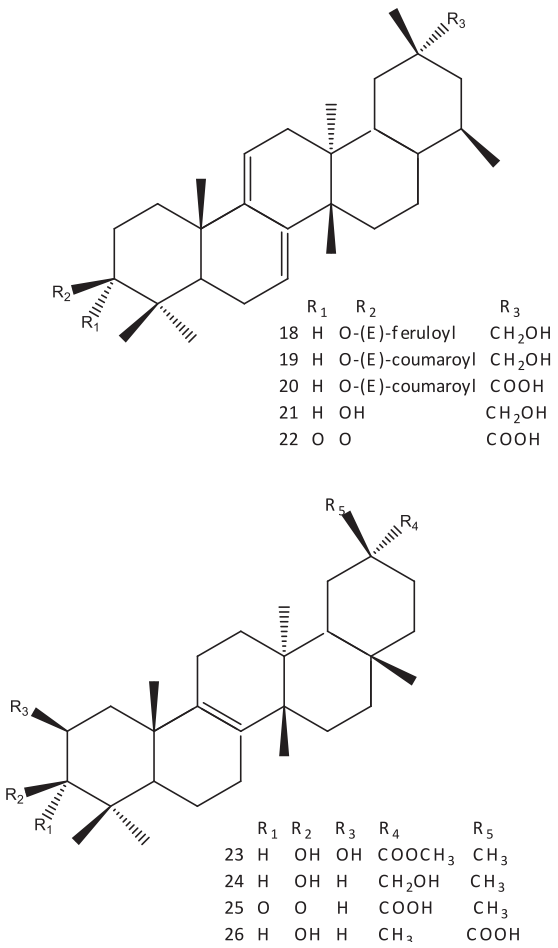

Figure 4. Structures of nine D:C friedooleanane type triterpenes isolated from the stem of *Lagenaria siceraria* (Molina) Standl.

CONCLUSION

The letter of Pero Vaz de Caminha, considered as Brazil's birth certificate, describes in few pages the first impression of the new colony. The Portuguese left the new land some days after their arrival. They did not collect any plant for further identification and even less mentioned their medicinal uses.

It was the naturalists who visited Brazil from the 16th to 19th century who described botanically and therapeutically medicinal plants they found in their journeys to the interior of the country. They left their records in form of books and diaries which still are as a fundamental source of Brazilian natural history (Alves 2010, 2013).

From the letter of Caminha, *Bixa orellana* and *Genipa americana* have now been unequivocally identified as the tinctures the Indians painted their bodies. However, the identification of the most of the plants mentioned by Caminha is an open question. According to Andrade Lima (1984) and Filgueiras and Peixoto (2002), the reference to the 'water gourds the Indians carried out is likely to be the fruits of *Lagenaria siceraria*.

Caminha also described how one man was wearing a sort of wig made of yellow bird feathers, glued to his hair with a material as soft as wax, but which was not wax. This 'wax' seems to be the resin of almecega, *Protium heptaphyllum* (Andrade-Lima 1974; Filgueiras and Peixoto 2002).

The progress in chemistry and pharmacology showed the potential of their constituents as therapeutic agents.

Despite the structural differences in the main constituents of bixin, genipin and α– and β-amyrin, they show similar therapeutic activities. The mechanism of action responsible for these properties is well known and was discussed in this article.

It is worth noting that most of the works developed with such plants have been produced in Asia. Special attention should be given by Brazilian scientists to these historical plants. Further studies are needed to evaluate the pharmacological and phytochemical activities of other plants mentioned by Caminha.

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