Bioactive Phytochemical Constituents of Some Edible Fruits of Myrtaceae Family

Mohammad Asif

Department of Pharmacy, GRD (PG) IMT, Dehradun, 248009 Uttarakhand, India

Abstract
Many species of Myrtaceae family are cultivated throughout the tropics for their edible fruit, food products and also used as traditional medicines in various ailments such as inflammation, intestinal disorders, high blood pressure, diabetes, asthma, antimicrobials, antiscorbutics, carminatives, diuretics, and astringents. Common phenolic compounds are cyanidin 3-glucoside, delphinidin 3-glucoside, ellagic acid, kaempferol, myricetin, quercetin, quercitrin, and rutin in edible Myrtaceae fruits. The ethnomedical and phytochemical properties are study of these bioactive constituents of these fruits.

Keywords: Bioactive phytochemicals; Myrtaceae; traditional medicines

Academic Editor: Sihua Peng, Shanghai Ocean University, China

Received: February 10, 2015; Accepted: April 20, 2015; Published: May 30, 2015

Competing Interests: The authors have declared that no competing interests exist.

Consent: We confirm that the patient has given the informed consent for the casereport to be published.

Copyright: 2015 Asif Met al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

*Correspondence to: Mohammad Asif, Department of Pharmacy, GRD (PG) IMT, Dehradun, 248009 Uttarakhand, India
Email:aasif321@gmail.com
Introduction

The chemistry of natural products is very important and can be used in the search for bioactive compounds, such as polyphenols, flavonoids, glycosides. Flavonoids are ever-present in the higher plants. Anthocyanins can occur in any part of a plant; different parts of the same plant can have different anthocyanin pigments. Leaves and fruits tend to have simpler pigments than flowers. Complex pigments with several glycosylations are more stable to light degradation and enzymatic attack. Anthocyanin content of fruits tends to increase as the fruit matures, becoming complexed with metals and other flavonoids. The most common anthocyanidin is cyaniding (Silva. 1997; Reynertson, et al., 2005). The next two most common anthocyanidins are delphinidin and pelargonidin. There must be a considerable number of new anthocyanin. Species closely related to plants containing known polyphenolic antioxidants are likely to have similar polyphenolic constituents. The phytochemistry of one plant may serve as clues for related plants. Researchers looking for new antioxidants can, however, use ethnomedicinal information, paying special attention to plants that are used for illnesses or conditions that are ameliorated by compounds linked to antioxidant activity. Polyphenolics are diverse in their biological activities, so ethnomedical information that hints at polyphenolic contents.

The Myrtaceae is a large, well-defined family, with about 140 genera and about 4000 species. The capsular-fruited subfamily Leptospermoideae includes the well-known genus Eucalyptus. The fleshy-fruited subfamily Myroideae includes many economically important food and agriculture plants. Edible fruits and useful spices, including guava (Psidium spp.), clove (Syzygium aromaticum), allspice (Pimenta dioica), and bay rum (Pimenta racemosa) are all included in the subfamily Myroidea. Historically, the Myroidea was divided into three subtribes, but most researchers now believe that this division is artificial. The old subtribe Eugeniinae represents many of the edible fruits, but molecular and morphological evidence supports the argument that this taxon is polyphyletic (van der Merwe, et al., 2005; Bohte, and Drinnan. 2005; Drinnan, and Carrucan. 2005; Ladiges, and Udovicic. 2005; Wilson, et al., 2001; Lucas, et al., 2005) The genus Eugenia is now generally considered the neotropical group, and the plants designated Syzygium are considered which falls into the Acmena clade, distinct from Eugenia. This suggests that the fleshy-fruit character has developed more than once in the family (Wilson, et al., 2001; Lucas, et al., 2005). The genus Myrciaria is closely allied with Eugenia.

Phytochemistry and Ethnobotany

The whole family is characterized by leathery glandular leaves containing viscous aromatic terpenoid and polyphenolic substances and flowers with numerous stamens. The edible fruits produced by the subfamily Myroidea are often described by their bright anthocyanin colors, including orange, red, purple, and black (dark purple). They are sweet to tart, and aromatic; many are somewhat astringent, indicating the presence of tannins. The taste is often described as somewhat acid. New shoot growth for many species is wine-colored (Facciola. 1998), suggesting a high anthocyanin content in the leaves as well. Many known antioxidant flavonoids have been isolated from this group. Haron et al. (Haron, et al., 1992) found that leaf extracts of 17 Neotropical and Paleotropical Eugenia species contained myricetin, quercetin was present in 71% and kaempferol was present in 24%. Ellagic acid, methyllellagic acid, procyanidin, and
prodelphinidin have been found in many species in the family (Nair, et al., 1999). In dicots, ellagic acid is usually confined to certain families and plants containing trihydroxy flavonoids, just as caffeic and \( p \)-coumaric acid are found along with corresponding di- and monohydroxy flavonoids. Theoduloz showed that flavonoids in the five species of the Myrtaceae tested inhibit xanthine oxidase activity; this activity to the presence of the flavonoids quercitrin, quercetin, myricitrin, and myricetin. Surinam cherry (E. uniflora) is widely regarded as one of the best tasting of the Eugenia species, and the fruits average about 3 cm in size. They have a characteristic ribbed appearance, and several cultivars have been developed with fruits ranging from orange to crimson to black (Facciola. 1998). There is an extensive amount of literature documenting the ethnomedical uses of the leaves of Surinam cherry (Consolini, et al., 1999; Duke. 2000), and most of the phytochemical work has subsequently focused on characterizing the essential oil of the leaves. Ascorbic acid, \( \beta \)-carotene, and a few sesquiterpenes have been identified from the fruits (Duke. 2000). In unpublished studies from our lab, the Surinam cherry was found to contain cyanidin 3-glucoside, delphinidin 3-glucoside, dihydro myricetin, quercitrin, and quercetin 3-arabinoside. Several well-known antioxidant flavonoids have been reported from leaf extracts, including myricetin, myricitrin, gallocatechin, quercetin, and quercitin as well as the tannins eugeniflorin D-1 and D-2 (Lee, et al., 1997). Popenoe notes that the Brazilians prepare a liqueur from the fruits, and consider syrups and wines to have a medicinal value. In Madeira, fruits of E. uniflora are eaten for intestinal troubles (Rivera, and Obón. 1995). Fruits and leaves are also used for their astringent qualities, and to treat high blood pressure. Water decoctions of E. uniflora leaves are used in Paraguay to lower cholesterol and blood pressure, and have a highly significant anti-inflammatory action (Schapoval, et al., 1994). Ferro showed that leaf extracts were slightly active on lipid metabolism, and may exert a protective effect on triglycerides and very low-density lipoprotein levels. Other fruits in this subfamily are also colorful, with an extensive ethnobotanical and ethnomedical use that suggests a possible flavonoid content. Syzygium jambos fruit is used as a tonic for the brain and for liver problems, as an astringent, and digestive and diuretic. The leaves contain seventeen different flavonoids (Constant, et al., 1997) and are used as an anesthetic, anti-inflammatory, and astringent, for apoplexy, asthma, bronchitis, cough, diabetes, dysentery, influenza, and rheumatism (Rivera, and Obón. 1995). Syzygium samarangense, which is cultivated in India for its edible fruit, contains two flavonol glycosides as well as EGCG, epicatechin 3-O-gallate, and samarangenins A and B (Harborne, and Baxter. 1999). In Taiwan, the flowers, which contain tannins, are used to treat fever and halt diarrhea. Flowers also contain desmethoxymatteucinol, 5-O-methyl-4′-desmethoxymatteucinol, oleic acid, and \( \beta \)-sitosterol. The jaboticaba (Myrciaria cauliflora) is a popular edible in Brazil, much like grapes in the United States. The fruits are a dark red to maroon-purple and black, and are used to make jam, tarts, strong wines, and liqueurs. In addition, decoctions of the sun-dried skins have been used for a variety of inflammatory conditions, including hemoptysis, asthma, diarrhea, and tonsillitis. E. aggregata is a popular reddish-purple edible in Brazil, eaten fresh or used to make jams and jellies (Facciola. 1998) which has not been phytochemically examined.

**Antioxidants, Anti-inflammatories, and Disease Chemoprevention**

2000; Rahman, and Adcock. 2006). Natural antioxidants and anti-inflammatories from fruits and vegetables are implicated as protective constituents of these foods by providing a measure of protection that slows the processes of oxidative damage and mediates inflammation (van Poppel, et al., 1994; Hollman, and Katan. 1999). The antioxidant and anti-inflammatory properties of several edible fruits produced by species in three genera Eugenia, Myrciaria, and Syzygium of the plant family Myrtaceae.

**Oxidative Damage and Dietary Antioxidants**

Free radicals and reactive oxygen species (ROS) are produced naturally through mitochondrial oxidative metabolism and are present in many environmental pollutants. Free radicals and ROS damage cell membranes, and oxidation of low-density lipoprotein (LDL) is a major factor in the promotion of CHD. Carcinogenesis may also be initiated through oxidatively-induced DNA damage (Jacob, and Burri. 1996; Steinberg. 1997). Oxidative damage is balanced by endogenous antioxidants, but additional protection provided by nutritive and non-nutritive elements from food are critical in disease chemoprevention. Repeated damage caused by ROS throughout the span of a human life increases with time, and is a major cause of age-related cancers and other oxidatively-induced diseases. Research in natural antioxidants is becoming increasingly important both in understanding the beneficial aspects of plant-based foods and in improving the quality of fatty foods. Antioxidants are routinely used by the industry to prevent the oxidation of food in storage and inhibit rancidity. The well-known vitamin antioxidants in food include ascorbic acid, β-carotene, and α-tocopherol. Many clinical and epidemiological studies have sought to demonstrate the efficacy of these vitamins in preventing a wide variety of diseases (Blumenthal, et al., 2000; Giugliano. 2000; Haegel, et al., 2000). However, some of these studies failed to show significant antioxidative protection *in vitro* (Pellegrini, et al., 2000; Scheen. 2000), which suggests that vitamins obtained via whole food or by a balanced diet may be more effective than supplements, possibly through synergistic interactions with other compounds.

**Phenolics as Antioxidant Agents**

There is now a strong consensus that flavonoids and related polyphenols are responsible for much of the antioxidant activity of fruits and vegetables (Frankel, et al., 1993; Vinson, et al., 1999). Many fruits and vegetables are high in flavonoid content. Flavonoids impart color and taste to flowers and fruits, and it is estimated that humans consume between a few hundred milligrams and one gram of flavonoids every day (Pietta. 2000; Hollman, and Katan. 1999). Green tea (*Camellia sinensis*) has received widespread research attention based in part on epidemiological evidence suggesting that cultures that use the beverage show lower incidence of oxidatively-induced disease. Tea is rich in pharmacologically active flavon-3-ols like epigallocatechin-3-gallate (EGCG); these catechins can account for 35-52% of green tea solid extract (Tang, and Meydani. 2001). Flavonoids appear in blood plasma at pharmacologically active levels after eating flavonoid-rich foods, but do not accumulate in the body (Cao, et al., 1998). Consuming flavonoids regularly increases longevity by reducing inflammation and contributing to the amelioration of atherosclerosis from CHD (Frankel, et al., 1993). The range of flavonoid biological activity is large; in addition to scavenging free radicals and ROS, flavonoids have been shown to be anti-inflammatory, antiallergenic, antiviral, antibacterial, antifungal, antitumor, and antihemorrhagic (Formica, and Regelson.1995; Slowing, et al., 1996). It has been hypothesized that flavonoids have been produced by plants for over one billion years, and that this continuous co-evolution with animals has led to the extraordinary diversity of biochemical and pharmacological activities in human systems. Flavonoids
inhibit a number of oxidative enzymes, including aldose reductase, α-glucosidase, xanthine oxidase, monoxygenase, lipoxygenase and cyclooxygenase (Yoshikawa, et al., 1998). Plant polyphenols interact with LDL, enriching and protecting it from oxidation when entering the bloodstream. The so-called “French Paradox” refers to the fact that despite the high fat content of the French diet, there is a lower incidence of CHD in France than in countries where fat intake is similar. This has been attributed to the high polyphenolic content of red wine and other fruits and vegetables prevalent in the French and “Mediterranean diet” (Burns, et al., 2000).

There are over 4000 naturally occurring flavonoids in several subclasses. All have the same basic C₆-C₃-C₆ phenolic carbon skeleton. Flavonoids are ubiquitous in the higher plants and play an ecological as well as physiological role. The anthocyanins are the most important flower and fruit pigments; they attract pollinators and seed dispersers and protect plant tissues from ultraviolet (UV) radiation damage. Some flavonoids mediate enzyme inhibition, act as antifeedants to herbivorous pests and defense compounds against infection, and play roles in photosynthesis, energy transfer, control of respiration, and the biosynthesis of toxic compounds (Middleton, et al., 2000). Flavonols and isoflavones are responsible for the chemical signaling involved in leguminous root node formation (Begum, et al., 2001; Harborne, and Baxter. 1999). Studies suggest that the antioxidant potential of phenolics is mainly due to their ability to act as reducing agents (Kähkönen, et al., 1999). It is well established that the efficacy of flavonoids as antioxidants stems from the number and position of the hydroxyl substitutions on the basic structure; an increase in number of hydroxyl groups is directly correlated with increasing activity, and the 3′,4′-dihydroxy substitution is significant (Cao, et al., 1997; Rice-Evans, et al., 1997). Pigmented berries and other fruits like blueberries, cranberries, strawberries, grapes, and currants are of great interest for among the other phenolic compounds, they are rich in anthocyanins. Anthocyanins are the glycosides of anthocyanidins, and contribute greatly to the orange, red and blue colors in fruits and flowers. Berries and other tropical fruits grow under conditions of high oxidative stress (intense sunlight and high heat), and produce anthocyanins and other protective phenolic compounds that inhibit lipid peroxidation and

Figure 1: Chemical structures of the most common flavonoids.
ultraviolet damage in plant tissues. In humans, anthocyanins have a strong antioxidant, anti-inflammatory, antimutagenic, and cancer chemopreventative activities (Kong, et al., 2003).

![Chemical Structures of Six Common Anthocyanidins](image)

**Figure 2** Chemical structures of six common anthocyanidins.

### Cytokines and Chronic Inflammation

Inflammation is characterized by the recruitment and accumulation of neutrophil leukocytes in biological tissues after injury or assault in a process called chemotaxis. Neutrophils are recruited from blood by a number of inflammatory chemotactic cytokines (chemokines). Chemokines are heparin-binding proteins circumscribed by four chemokine families, of which two have been extensively characterized. The two well-studied groups are distinguished by the position of the first two cysteines: either adjacent (CC chemokines), or separated by one amino acid (CXC chemokines). Interleukin (IL)-8 is a member of the CXC chemokine family, with a molecular weight of about 8 kD. A glutamic acid-leucine-arginine (ERL) sequence near the N-terminal found in IL-8 and related chemokines has been linked to the neutrophil chemotactic function. The IL-8 is a prototypic inflammatory mediator that plays a key role in neutrophil recruitment. Many stress factors and cellular stimuli induce production of IL-8, including tumor necrosis factor-α (TNF-α), IL-1, nuclear factor (NF)-κB, activator protein (AP)-1, hypoxia, acidosis, nitric oxide and cell density. The promoter region of the IL-8 gene contains a binding site for NF-κB, a redox-responsive transcription factor normally found in the cytoplasm. NF-κB is a sort of master switch for many pro-inflammatory mechanisms. Normally bound with the inhibitory protein IκB, NF-κB becomes activated when IκB is phosphorylated by IκB kinase (Kim et al., 2006). IL-8 is not a constitutive peptide, rather it occurs in response to inflammatory stimuli (Harada, et al., 1994). Many different cell types can produce IL-8 when stimulated, including neutrophils themselves, the result being that they further intensify neutrophil recruitment to sites of inflammation in any type of tissue. This sort of possible feedback loop may amplify and protract the inflammatory response. The fact that IL-8 is generated by tissue cells is important to the etiology of many different inflammatory conditions: rhinitis, bronchitis, pulmonary fibrosis, psoriasis, and inflammatory bowel disease (Kim et al., 2006). Chronic inflammation has also been implicated in CHD, cancers, neurodegenerative diseases and chronic inflammatory conditions like chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, and chronic asthma. Elevated levels of IL-8 contribute to cancer progression by functioning as a mitogenic, angiogenic, and
motogenic factor (Xie. 2001). Many tumor cells express IL-8 constitutively and the expression level appears to correlate with tumorigenic and metastatic potential.

**Phenolics as Anti-inflammatories**

Anti-inflammatory activity is not strictly correlated with antioxidant activity, even though there is some overlap. Flavonoids act on several different synergistic pathways as both antioxidants and anti-inflammatories. ROS can initiate transcription factors like NF-κB and AP-1, as well as signal-transduction pathways like mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI-3K) (Rahman, and Adcock. 2006). The activation of these pro-inflammatory mediators enhances transcription of downstream inflammatory chemokines (Calixto, et al., 2004). By reducing the oxidative attack, flavonoids reduce the amount of activated NF-κB, which is directly tied to IL-8 production. They also inhibit the degradation of IxkB, reducing the amount of activated NF-κB. It is not clear whether these are the direct mechanisms involved in flavonoid ability to inhibit IL-8 production, or whether they represent a complementary or synergistic mechanism acting to inhibit IL-8 chemokine production. Antioxidant green tea polyphenols, especially EGCG, have shown an ability to inhibit IL-8 production in inflammatory airway diseases (Kim et al., 2006). They also inhibit angiogenesis by decreasing DNA-binding ability of NF-κB by inhibiting phosphorylization and degradation of IxkB (Rodriguez, et al., 2006; Chen, et al., 2002). Luteolin has been shown to suppress TNF-α-induced IL-8 production in intestinal cells by inhibiting the phosphorylation of MAPK (Kim, et al., 2005). By inhibiting monoxygenase and lipoxygenase enzymes, flavonoids affect arachidonic acid metabolism, reducing eicosanoid production that can include pro-inflammatory prostaglandins and leukotrienes. Leukotriene B₄ is a potent chemo attractant involved in inflammation. In addition, flavonoids modulate the function of many inflammatory cells, including T lymphocytes, B lymphocytes, natural killer cells, macrophages and neutrophils. A comprehensive review of flavonoid bioactivity by Middleton et al. describes some 35 different enzymatic pathways involved in inflammatory mediation that are affected by flavonoids, including protein kinase C, phospholipase A₂, aromatase, xanthine oxidase, aldose reductase, and many more (Middleton, et al., 2000). Some of the most common and well-known anti-inflammatories are steroidal compounds. Steroids, however, often have unwanted effects on the endocrine system as hormonal modulators. Some chronic inflammatory conditions like COPD are virtually steroid-resistant, and it has been noted that non-steroidal anti-inflammatories that target chemokine pathways are needed as new therapies (Biswas, et al., 2005; de Boer, 2002).

The jaboticaba (Myrciaria cauliflora (Myrtaceae)) is used as a treatment for hemoptysis, asthma, diarrhea, and gargled for chronic inflammation of the tonsils. The jaboticaba (no species distinguished) has been reported to contain tannins, and we previously reported the presence of cyanidin 3-glucoside (3) in M. cauliflora (Einbond, et al., 2004). M. jaboticaba reportedly contains peonidin 3-glucoside and its aglycone, and the related camu-camu berry (M. dubia), an edible fruit known for its high levels of ascorbic acid, contains 3 and delphinidin 3-glucoside (4) as the main pigments (Zanatta, et al., 2005). The antioxidant, anti-inflammatory and potential anticancer compounds obtained from edible fruits of jaboticaba. Crude methanolic extracts were shown to have strong antiradical activity. Fruit extracts were subsequently subjected to activity-guided fractionation resulting in the isolation of a new depside, jaboticabin (1). In addition, the related depside 2-O-(3,4-dihydroxybenzoyl)-2,4,6-trihydroxyphenylacetic acid (2), 4, pyranocyanin B, quercetin, isoquercitrin, quercimeritrin, quercitrin, rutin, myricitrin, cinnamic acid, o-coumaric acid, gallic acid, protocatechuic acid (5), methyl protocatechuate, and ellagic acid were identified from this species for the first time.
### Compounds

1. Jaboticabin
   - R: CH₃

2. 2-O-(3,4-dihydroxybenzoyl)-2,4,6-trihydroxyphenyl acetic acid

3. Cyanidin 3-glucoside
   - R: H

4. Delphinidin 3-glucoside
   - R: OH

### Compounds

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>CH₃</td>
</tr>
<tr>
<td>OH</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
</tr>
</tbody>
</table>

5. Protocatechic acid
6. Methylprotocatechuare
7. Gallic acid

### Compounds

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>OH</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

8. Cinnamic acid
9. O-coumaric acid

### Compounds

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

10. Quercetin
11. Quercitrin
12. Isoquercitrin
13. Rutin
14. Myricitrin
15. Quercimeritrin

### Ellagic acid

- HO-OC₆H₄-COOH
The phenolic compounds with potential for development as anti-inflammatories and COPD therapeutics. In addition to the depsides, which occur as minor constituents of the fruit, there is a high concentration of anthocyanins, particularly cyanidin 3-glucoside and delphinidin 3-glucoside. These two anthocyanins are common flower and fruit pigments, and yet their antioxidant and anti-inflammatory activity is significant. They are strong antiirradical compounds in the DPPH assay. The jaboticaba also contains many flavonols and phenolic acids with documented antioxidant and anti-inflammatory activities. The jaboticaba compounds can inhibit the production of IL-8, a potent chemokine neutrophil attractant. Neutrophil recruitment is one of the hallmarks of inflammation, and the ability of jaboticaba phenolics to inhibit the production of IL-8 is a significant anti-inflammatory mechanism. In addition, some depsides are very potent non-steroidal anti-inflammatories in that they inhibit the biosynthesis of prostaglandin and LTB4 (Kumar and Muller. 1999; Kumar and Muller. 2000). These pro-inflammatory eicosanoid mediators are the result of arachidonic acid metabolism, which has been shown to be affected by flavonoids that inhibit COX and LOX enzymes. In addition to these phenolics, there are many ellagitannins in jaboticaba that remain unidentified. Ellagitannins are responsible for much of the beneficial effects of strawberries (Aaby, et al., 2005) and pomegranate juice (Cerda, et al., 2004; Seeram, et al., 2005; Seeram, et al., 2004).

Depsides are phenolic compounds composed of two or more monocyclic aromatic units linked by an ester bond. They are most often found in lichens, but have also been isolated from higher plants, including species of the Ericaceae, Lamiaceae, and Papaveraceae (Ono, et al., 2002; Gowniak. 2001; Hillenbrand, et al.2004). They have not been previously reported in the Myrtaceae. Depsides have antibiotic, anti-HIV, and antiproliferative activity (Kumar et al., 1999). As inhibitors of prostaglandin biosynthesis and leukotriene B4 biosynthesis, depsides are potent non-steroidal anti-inflammatories (Kumar and Muller. 2000). Compound 1 was as a reddish amorphous powder and comparison with 2 confirmed the structure of jaboticabin (1) as methyl 2-(3,4-dihydroxybenzoyloxy)-4,6-dihydroxyphenyl)acetate. An ethanolic extract of jaboticaba fruits was that 1 could be a methyl ester artifact from the initial MeOH extraction. Compounds 2-5, pyranocyanin B, methyl protocatechuate, ellagic acid, quercimeritrin, and quercitrin were isolated (Hillenbrand, et al.,2004; Yu, et al., 2000; Seeram, et al., 2006; Miyazawa, et al., 2003; Sang, et al., 2002).

Depsides 1 and 2 exhibited antiradical activity in the DPPH assay, colon cancer cell cytotoxicity, and significantly inhibited chemokine interleukin (IL)-8 production in human small airway epithelial (SAE) cells before and after treatment with cigarette smoke extract (CSE). Compound 1 decreased IL-8 production in untreated SAE cells by 81.3%, and decreased production in SAE cells treated with 5% CSE by 47.3%. Compound 2 inhibited IL-8 production by 74.9% in untreated SAE cells and 70.3% in treated SAE cells. Compound 5 also inhibited IL-8 production, but not to the same degree as the depsides. This indicates that either the dimeric structure or the phloroglucinol moiety, with or without the methyl ethanoate group, is important for activity. The anthocyanins 3 and 4, major constituents of jaboticaba fruits, also displayed significant activity against IL-8 production in SAE cells. IL-8 was not detected in SAE cells treated with compound 4, which caused a 96% reduction of IL-8 production in SAE cells treated with CSE; compound 3 inhibited IL-8 production by 65.3% and 36.4%, respectively. Compounds 1-5 were more effective at blocking IL-8 production in untreated SAE cells than catechin, and 2 and 4 were more effective than catechin at blocking cigarette smoke-induced inflammation.
Airway epithelial cells play a crucial role in chronic airway inflammatory diseases, and are an important target for therapeutic intervention (Takizawa, 1998). IL-8 is a chemotactic cytokine (chemokine) implicated in some cancers and a wide range of chronic inflammatory conditions, including rheumatoid arthritis, and heart and lung diseases (Koefler, et al., 2005). IL-8 is a powerful chemoattractant for neutrophils; the recruitment and accumulation neutrophils is a hallmark of inflammation. The ability of compounds 1-5 to reduce IL-8 production suggests an important anti-inflammatory action of these compounds. Similar compounds have been shown to inhibit the initiation of related inflammatory pathways, including NF-κB, TNF-α, AP-1, and LTB₄ biosynthesis (Kim et al., 2006). The COPD is a complex lung disease characterized by irreversible airflow obstruction due to chronic inflammation, and characterized by an accumulation of neutrophils in lung cells and tissues. COPD includes chronic obstructive bronchiolitis (fibrosis and obstruction of small airways) and emphysema (permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of lung parenchyma). The non-steroidal anti-inflammatories that target chemokine pathways are needed as new therapies for COPD, as it is generally considered steroid-resistant (Biswa, et al., 2005; de Boer, 2002; Barnes, 2001). The demonstration that jaboticaba depsides, phenolic acids, and anthocyanins can reduce inflammation secondary to smoke exposure could provide a novel therapeutic role for these compounds in COPD. The cytotoxicity of 1, 2, and 4 is comparable to IC₅₀ values for 5-fluorouracil (5-FU), a drug used for colon cancer treatment, epigallocatechin gallate (EGCG), and Polyphenon E (Poly E), a standardized decaffeinated green tea extract (Yang, et al., 2005; Shimizu, et al., 2005). Compound 1 is cytotoxic against HT29 colon cancer cells, and 2 is cytotoxic against HCT116 colon cancer cells. Consistent with published literature, 4 was more cytotoxic than 3 (Marko, et al., 2004; Meiers, et al., 2001). Compound 4 showed good activity against both the HCT116 and SW480 cell lines, while 3 inhibited 50% cell growth only at the 100 μM range. Pyranocyanin B was not significantly cytotoxic against any of the colon cancer cells lines tested. Compounds 1-4 also exhibit good antiradical activity. The anthocyanins are a group of well-studied phenolic compounds with antioxidant, anti-inflammatory, antimutagenic, and cancer chemopreventative activities (Kong, et al., 2003). The jaboticaba anthocyanins and depsides exhibit good antiradical activity, cytotoxicity, and inhibit IL-8 production in both untreated SAE cells and those treated with pro-inflammatory CSE. Depsides from foods and botanicals are less well-studied than the anthocyanins, possibly as a result of their limited distribution in higher plants, and this is the first report of their ability to inhibit IL-8 production and cytotoxicity against colon cancer cells. The jaboticaba is rich in anthocyanins, phenolic acids, flavonoids, and contains depsides with antiradical, anti-inflammatory and cytotoxic activity, and therefore it may be a good candidate for development in larger-scale agriculture and has the potential to be developed as a functional food.

The leaves in this taxon are typically fragrant, and most of the phytochemical work on these species concerns those aromatic terpenoids (Guedes, et al., 2004; Hoang, and Nguyen, 2004). In addition to their use as food, many of these fruits have been used in divergent traditional medical practices for a variety of illnesses and conditions. Most notably, the seeds of the jamun (S. cumini) are an important Ayurvedic medicine for diabetes. The rose apple (S. jambos) has been used in India as a tonic for the brain and for liver problems, as an astringent, and digestive, and distilled to make rosewater. In Brazil, E. brasilienis leaves have been used for gastrointestinal disorders and rheumatism, and the jaboticaba fruit (M. caulisflora) has been used as a treatment for hemoptysis, asthma, diarrhea, and chronic inflammation of the tonsils. Other related Myrtoideae fruits not analyzed here have been used for several inflammatory conditions, including sore throat, high blood pressure, ringworm, and as an antimicrobial, antiscorbutic, carminative, diuretic, and astringent (Rivera, and Obón, 1995). Dark-colored fruits have generated...
considerable interest as a rich source of phenolic antioxidants. Blueberries, cranberries, strawberries, grapes, cherries, and other temperate fruits have been the subject of many studies and analyses (Zheng, and Wang. 2003; Wang, et al., 1999; Kähkönen et al., 2001). The anthocyanins, strong antioxidants and anti-inflammatories, with antimutagenic and cancer chemopreventative activities (Reynertson, et al., 2006), are the most abundant compounds among those quantified and are largely responsible for the bright colors of these fruits. Many of the fruits analyzed are high in both total phenolics and anthocyanins. (Prior, et al., 2005), as the camu-camu berry is known to contain one of the highest levels of ascorbic acid of any fruit (Aragao, et al., 1996). Antiradical activity ranges from very active (M. cauliflora) to inactive (S. cumini). M. cauliflora is the most active fruit extract. Many of these species contain ellagitannins and flavonoids that may influence antioxidant activity.

Cyanidin 3-glucoside (1) is the most abundant compound in E. aggregata, E. brasiliensis, M. cauliflora, M. vexator, S. curranii, S. malaccense, and S. samarangense var. Taiwan pink. It was detected or quantified in all but the two species that do not produce fruit colored dark purple or red; the orange fruit of E. luschnathiana and yellow fruit of S. jambos have no detectable anthocyanins. The purple-skinned fruits E. brasiliensis, E. aggregata, M. cauliflora, M. vexator, S. curranii, and S. cumini contain both 1 and delphinidin 3-glucoside (2) and are unsurprisingly the highest in TAC. The only reddish fruit that contains both 1 and 2 is M. dubia; the remaining red to pink fruits E. reinwardtiana, S. malaccense, S. samarangense, and S. samarangense var. Taiwan pink contain only 1. Syzygium curranii has far higher levels of delphinidin 3-glucoside than any other fruit. Syzygium cumini, which is used by Ayurvedic practitioners in India as an antidiabetic medicine (Grover, et al., 2002), has more 2 than 1. Fruit contains several delphinidin glycosides. Compound 2 is a potent antiradical compound. Seed extracts of S. cumini, the part most often used in Ayurvedic medicine, were previously shown to have high levels of total phenolics and good activity (Luximon-Ramma, et al., 2003).

Discussion and Conclusion

The phenolic content and antioxidant potential of edible fruits are useful in understanding the role that these factors play in health and disease chemoprevention (Minino, et al., 2006). Plant-based diets are inversely correlated with cardiac and cancer diseases (Youdim, and Joseph. 2001; Goodwin, and Brodwick. 1995), a comprehensive understanding of the phytochemicals in edible fruits and vegetables is crucial to developing better diets and healthier lives. The biological damage from inflammation and oxidative assault is cumulative, and incidence of disease increases over a lifetime. A measure of protection is provided by diets high in foods that supply beneficial phytochemicals. While the benefits of many popular foods and beverages (i.e. green tea (Rodriguez, et al., 2006; Chen, et al., 2002) and wine (de Gaulejac, et al.,1999) have been documented, there are thousands of “underutilized” fruits and vegetables that may confer as good or better chemoprevention than those well-studied foods. The plant family Myrtaceae is pan-tropical, with concentrations in South America, Southeast Asia, and Australia. The fleshy-fruited subfamily Myrtoideae includes many economically important food plants, agricultural crops, and ornamentals, specifically the genus Myrtus (myrtle), spices such as clove (Syzygium aromaticum), allspice (Pimenta dioica), and bay rum (Pimenta racemosa), and the fruits of Psidium (guavas). The camu-camu berry (Myrciaria dubia) has become important as a functional food, and can be found on the shelves of many health food stores as a dietary supplement due to the high levels of ascorbic acid in the fruit.
References

18. de Boer WI. Cytokines and therapy in COPD. *Chest* 2002, 121: 209S-218S
64. Pellegrini N, Riso P, PorriNNI M. Tomato consumption does not affect the total antioxidant capacity of plasma. *Nut*. 2000, 16: 268-271
76. Seeram NP, Adams LS, Henning SM, Niu Y, Zhang Y, Nair MG, Heber D. In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total
pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. *J Nut Biochem.* 2005, 16: 360-367


82. Steinberg D. A critical look at the evidence for the oxidation of LDL in atherogenesis. *Atherosclerosis.* 1997, 131: S5-S7


