REVIEW

Major Australian tropical fruits biodiversity: Bioactive compounds and their bioactivities

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The plant kingdom harbours many diverse bioactive molecules of pharmacological relevance. Temperate fruits and vegetables have been highly studied in this regard, but there have been fewer studies of fruits and vegetables from the tropics. As global consumers demand and are prepared to pay for new appealing and exotic foods, tropical fruits are now being more intensively investigated. Polyphenols and major classes of compounds like flavonoids or carotenoids are ubiquitously present in these fruits, as they are in the temperate ones, but particular classes of compounds are unique to tropical fruits and other plant parts. Bioactivity studies of compounds specific to tropical fruit plants may lead to new drug discoveries, while the synergistic action of the wide range of diverse compounds contained in plant extracts underlies nutritional and health properties of tropical fruits and vegetables. The evidence for in vitro and animal bioactivities is a strong indicator of the pharmacological promise shown in tropical fruit plant biodiversity. In this review, we will discuss both the occurrence of potential bioactive compounds isolated and identified from a selection of tropical fruit plants of importance in Australia, as well as recent studies of bioactivity associated with such fruits and other fruit plant parts.

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1 Introduction

Extensive epidemiological studies have established that a balanced diet including plentiful consumption of fresh fruits and vegetables helps in maintaining a healthy life. Fruits and vegetables can have positive effects, decreasing the risks of both development and incidence of chronic diseases such as cardiovascular diseases, some types of cancers, arthritis and diabetes. These empirical observations, confirmed over the years with multiple studies [1–4], have led health authorities to promote the consumption of fruits and vegetables. It has also led to the development of marketing messages for specific fruits and vegetables, and a wide range of functional foods, fortified with fruit and vegetable extracts and components. Berries have attracted particular attention due to their very high content of antioxidant secondary metabolites [5].

Compared with fruits and vegetables grown in temperate regions of the world, tropical fruits, especially ones that originated in Asia, have been studied in much lesser detail. There is no formal scientific definition of tropical fruits. Although the word ''tropical'' would imply that they are cultivated in the tropics, many of these fruits are now cultivated throughout the world. In the preface of a special issue about exotic fruits, these plants were described as growing under a specific climate conditions and a very complex ecosystem [6].

Interest is growing in tropical fruit products, mainly because their attractive appearance and exotic taste appeals

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to consumers worldwide. Because of this new and emerging market, there is a growing demand and need for new studies regarding the consumption and health benefits of tropical fruits. However, when compared with common temperate fruits, there is a large gap to fill in order to compensate for the current lack of knowledge.

Major tropical fruit production was reported by the Food and Agriculture Organization (FAO) to be over 181 million tons in 2008 [7], with more than half of the overall production originating from Asia. This production is increasing at an average rate of 3% per year. Bananas are widely available on world markets with a total production of 93 million tonnes in 2008, while mango production rose by 25% from 2007, but was less than a third of that of bananas [7]. Due to a lack of both knowledge and communication of the wide variety of tropical fruits, the long distance to Western markets and generally short shelf life, many of these 'exotic' fruits remain largely unknown to consumers in many markets. In the context of a growing demand for new food products in both developed and emerging economies, tropical fruits offer considerable promise due to the current low level of usage outside their region of production.

Not only are such fruits appealing, but a number of them have been empirically used in ethnopharmacology or traditional medicine [8, 9], especially for common illnesses that occur in tropical and subtropical regions [10]. This suggests the possibility of nutritional benefits that could be harnessed to encourage consumption, although it is not known whether tropical fruits have a bioactive compounds profile that differs significantly from those of temperate fruits.

Some epidemiological studies have reported the impact of a diet rich in tropical fruits on population health. Ferguson et al. [11] report the evidence of colon cancer incidence being lower among Polynesians, whose diet is based on tropical fruits and plant-based foods, compared with Europeans, and how this incidence has changed now that processed food is becoming more common in the Polynesian diet. Although the reasons are controversial, such diet-level effects may be linked to the general anti-oxidant content of fruits; fruits are also rich sources of a range of secondary metabolites that may have specific effects on human metabolism. Numerous compounds isolated from natural sources in general, and from fruits in particular, are today lead compounds in the development of new therapeutic drugs. Resveratrol [12], quercetin [13] and lupeol [14] are just a few examples of natural fruit bioactive compounds.

These compounds have a general anti-oxidant activity but also other specific bioactivities such as anti-inflammatory/anti-proliferative effects or plasma sugar level regulation [15–17]. Identifying bioactive molecules is of major importance in understanding the underlying mechanisms of action and interactions of natural products in the human body. Although fruits cultivated in temperate parts of the world have already been and continue to be studied for their nutritional and health-promoting value, tropical fruits remain an expansive and potentially novel source of natural products. Our knowledge of such products has been growing rapidly due to new technologies for identification and high-throughput screening methods to assess bioactivities. However, there is still much work to be accomplished to characterize potential nutritional components in tropical fruit. In addition to bioactivities within edible fruits, realizing fruit nutritional benefits requires commercial production, which can be aided by additional uses of the plant/tree as a source of bioactive compounds from non-fruit tissues (bark, leaves, roots, etc). Hence, this review will describe the composition and/or bioactivities from both fruit and other plant parts of the major tropical fruits plants cultivated in northern Australia but relevant to much of the rest of the tropical world: Annonaceae family. *Artocarpus* genus, *Persea americana*, Musaceae family, *Psidium guajava*, *Citrus* genus, *Litchi chinensis*, *Mangifera indica*, *Garcinia mangostana*, *Carica papaya*, *Passiflora* genus, *Diospyros kaki*, *Ananas comosus*. In this review, we will discuss the following two areas:

(i) Compositional data on potential bioactive compounds isolated and identified from tropical fruit plants.
(ii) Tropical fruit plants of interest and recent bioactivity reports on fruits and other plant parts.

By reviewing the existing knowledge of phytochemicals contained in tropical fruit plants, together with pharmacological studies of natural extracts derived from these plants, we intend to show how diverse are tropical fruit plants. It is thus evident that they represent an exciting opportunity for new research, both in nutrition and in pharmacology.

2 Bioactive compounds identified in tropical fruit plants

Tropical fruit plants have frequently been reported to be used in folk medicine [18], with more emphasis being placed on some fruit plants like *Psidium guava* [19] or *G. mangostana* [20] with many traditional uses reported across the world, or on different plants from the *Passiflora* genus commonly reported as being used for their sedative and anxiolytic effects [21]. Although from a nutritional aspect, fruits are most commonly consumed, authors from these reviews link different parts of the plants to their use in traditional medicine. For this reason, it is important to identify compounds present across the tropical fruit plant kingdom, regardless of their tissue location (roots, heartwood, leaves, bark, flowers, fruit both skin and flesh, seeds). Bioactive compounds extracted from tropical fruit plants can be classified into a number of different chemical families. Although the identification of many bioactive compounds is becoming less problematic due to advances in the technologies used to determine the structure of bioactive

compounds (IR/UV, ^{1}H and ^{13}C NMR, HPLC, LC-MS, LC-MS-MS and other mass spectrometry techniques), the challenge of identifying the more structurally complex compounds, or those present at very low concentrations, remains. Synthetic standards are widely used to confirm structures of extracted bioactive compounds; the compounds reported herein have all been identified through different and unambiguous methods, and by comparison with standards where available. A significant number of bioactive compounds are related to the polyphenol class, which is largely responsible for the anti-oxidant activity. Polyphenols are also most frequently reported as the active principle of the many bioactive extracts that will be reported in Section 3.

2.1 Primary metabolites isolated from tropical fruit plants

Caffeoylquinic acids **1** and feruloylquinic acids **2** are chlorogenic acids. They are derivatives of *trans*-cinnamic acid **3**, and constituents of lignocellulose in plant cell walls. Because they are derived from the lignin biosynthesis pathway, they are found in most tropical fruits. Caffeoylquinic acids **1** or structural isomers have been found in plants of the Annonaceae family, *Artocarpus* genus, and in avocado, banana, guava, mango, persimmon and pineapple among other fruits [22, 23]. Feruloylquinic acids **2** have only been found in guava and mangosteen [22] (Fig. 1).

Gallic acid **4** is commonly found in tropical fruits, either by itself, as digallic or trigallic acids, or as part of numerous esters (gallates) in many part of the plants, including seeds [24] flowers [25], leaves [26], fruits [27] and fruit pulp [28]. Phenylprop-2-enoic acids (or cinnamic acids) **5** are also reported regularly. Derivatives of cinnamic acid **5** like ferulic acid **6** have been reported in *P. guajava* [26, 29] and *G. mangostana* [30]. In this latter article, mangosteen fruit was more thoroughly screened, and a number of benzoic acid derivatives identified are shown in Fig. 2. These include 3-hydroxybenzoic acid **7**, 4-hydroxybenzoic acid **8**, protocatechuic acid **9**, vanillic acid **10** and piperonylic acid **11**. More cinnamic acid derivatives are also reported, including *p*-coumaric acid **12**, caffeic acid **13** and ferulic acid **6** derivatives [30]. Such simple phenolic acids should be expected to be encountered across the whole flowering plant kingdom.

2.2 Polyphenols isolated from tropical fruit plants

Several classes of polyphenols exist, of differing complexities and structure. The simpler structures represent intermediates in the biosynthesis of more complex polyphenols. The major simple bioactive polyphenols are plant lignans (Fig. 3), which are common compounds in seeds, grains, vegetables and fruits. As described by Kuhnle et al. and

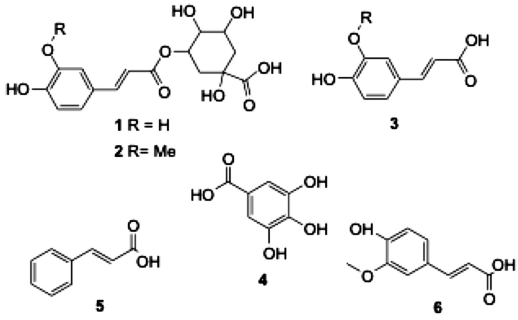


Figure 1. Primary metabolites.

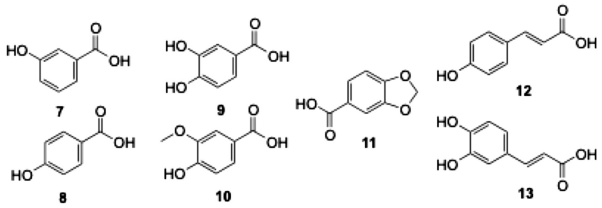


Figure 2. Benzoic acids derivatives from mangosteen.

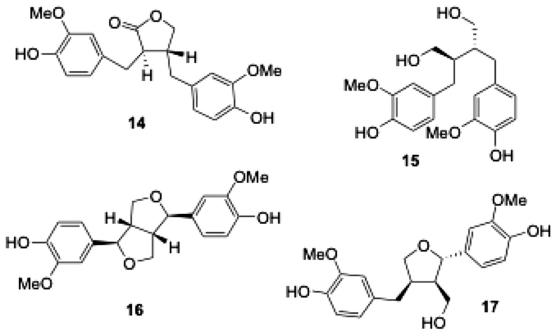


Figure 3. Lignans.

Thompson et al. [31, 32], multiple fruits and vegetables have been screened for nutrient content, including the main lignan matairesinol **14** (*P. americana*, *Musa* spp., *Dimocarpus longan*, *M. indica*, *C. papaya*, *D. kaki*, *A. comosus*), which is found jointly with secoisolariciresinol **15**. It is also no surprise to find their precursors pinoresinol **16** and lariciresinol **17** when fruits have been investigated for their presence. Lignans are expected to be found in all fruits as they are precursors to many secondary metabolites.

2.3 Secondary metabolites isolated from tropical fruit plants

Secondary polyphenol metabolites can also be classified into different families according to their structure.

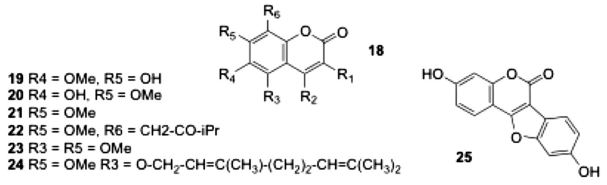


Figure 4. Coumarins.

2.3.1 Flavonoids

Flavonoid is the generic name given to compounds containing a benzopyrone moiety. If the benzopyrone is a benzopyrolactone, then the compounds belong to the coumarin derivatives subgroup. While coumarin is found in many plants, only derivatives of coumarin **18** are reviewed here (Fig. 4).

D. kaki has been reported as containing two coumarin derivatives, scopoletin **19** and isoscopoletin **20** [33]. *Citrus* species are a source of several linear coumarin derivatives [34–36]: herniarin **21** (methyl-umbelliferone), isoaurapten **22**, limetin **23**, 5-geranoxy-7-methoxycoumarin **24**.

Coumestrol **25** (3,9-dihydroxy-6*H*-Benzofuro[3,2-*c*][1]benzopyran-6-one) is a furanone derivative of coumarin. Its role as a phytoestrogen and as an analogue of estradiol makes it a notable compound. Its presence has been reported in *L. chinensis*, *Passiflora edulis*, *A. comosus* and *D. kaki* [31].

Psoralen **26** is a particularly important furanocoumarin known for its photoactivation (psoralen plus UVA or PUVA) in treating skin disorders (Fig. 5) [37]. Many derivatives of psoralen have been reported in *Citrus* species [38, 39] including: bergapten (5-methoxypsoralen) **28**, xanthotoxin (8-methoxypsoralen) **30**, isopimpinellin (5,8-dimethoxypsoralen) **31**, dihydroisopimpinellin (structure not fully defined), isoimperatorin (5-iso-pentenyloxypsoralen) **32**, imperatorin (8-iso-pentenyloxypsoralen) **33**, bergamotin (5-geranyloxy-psoralen) **34**, 8-geranyloxy-psoralen **35**, phellopterin (8-iso-pentenyloxypsoralen-5-methoxypsoralen) **36**, prangenin (9-[(3,3-dimethyloxiranyl) methoxy]-psoralen) **37**, isobyakangelicol (5-[(3,3-dimethyloxiranyl)-methoxy]-8-methoxypsoralen) **38**. All these compounds were identified with IR spectroscopy, melting point and by comparison with standards. Three furanocoumarin dimers, including paradisin A **41**, B **42** and C **43**, were also recently discovered in *Citrus* [40, 41]. In addition to these dimers, more derivatives of psoralen are listed with a greater certitude of their structure due to their identification using more advanced methodologies. These include bergaptol **27**, and 8-hydroxypsoralen **29**, (*R*)-6′,7′-dihydroxybergamottin **39**, (*R*)-bergamottin-6′,7′-epoxide **40** [40, 41].

In addition to the specific coumarin subfamily, benzopyrones are subdivided into three main groups: flavones, isoflavones and neoflavones. No neoflavones have been reported so far in tropical fruits.

2.3.2 Flavones

Flavones (Fig. 6–9) (cf. general structure **63–100)** or 2-phenylchromen-4-ones are found in *Artocarpus* species including a series of artoindonesianins (A2 **44**, E1 **58**, R **81**, U **53**, V **59**) [42, 43], artocarpetin **67**, norartocarpetin **65** as a demethylated artocapertin, as well as artocarpin **80**, norartocarpin **79** (demethylated artocarpin), cycloartocarpin **45** (cyclized artocarpin), artonin A **61**, and artonin B **62** [44]. Three other similar flavones have been reported: artocarpesin **73** [45], isoartocarpesin **74** [46], an isomer of artocarpesin, and cycloartocarpesin **51** [46], a cyclized artocarpesin. Flavones listed under the cudraflavone series have also been reported – cudraflavone A **55** [47] and B **52** [46, 48] as well as 5′-hydroxycudraflavone A **56** [42]. Cyclomorusin **60**, cycloheterophyllin **57** [47], cyclocommunin **46** [42, 47], brosimone I **49** [46], dihydrocycloartomunin **48** and dihydroisocycloartomunin **49** [47] complete the list of flavones that contain more than one flavonoid moiety. Many isoprenylated flavones also exist in plants. The following flavones: heterophyllin **54** [43], mulberrin **77** [48, 49], albanin A **75** [48], carpachromene **50** [46], apigenin **63** and 6-prenylapigenin **76** [48] have all been reported in *Artocarpus* species as isoprenylated flavones.

Citrus polymethoxyflavones have been reported and are the simplest flavones found overall [50]. These include tangeritin **68**, sinensetin **69**, isosinensetin **70**, 5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone **71** and 3,5,6,7,8,3′,4′-heptamethoxyflavone **72**. 6- or 8-C-glucoside flavones have been reported [51] such as isovitexin **83**, vicenin II **88** and diosmetin-6,8-di-C-glucoside **89**. Two arabino-glucopyranose derivatives have also been found, namely apigenin-6-C-[α-L-arabinopyranosyl-(1→6)]-*O*-β-D-glucopyranoside **90**, and apigenin-8-C-[α-L-arabinopyranosyl-(1→6)]-*O*-β-D-glucopyranoside **91**.

These compounds provide an indication that the glycosylated forms of polyphenols can be extremely varied and complex. The identification of such compounds is generally difficult due to the complexity of substituents and substitution patterns. In *Passiflora* spp., Dhawan et al. [21] reviewed a large list of such compounds. Two aglycone flavones are mainly reported: apigenin **63** and luteolin **64** along with many monosaccharide glycone forms such as isovitexin **82**, vitexin **83**, isoorientin **84**, orientin **85**, swertisin **87**, vicenin II **88**, schaftoside **92**, isoschaftoside **93** and 6,8-di-C-glycosylchrysin **94** but also disaccharides with isovitexin-2″-*O*-glucopyranoside **95** and isoorientin-2″-*O*-glucopyranoside **96**. Most of these compounds have since been reported again along with spinosin **99** [52, 53] and disaccharides luteolin-7-*O*-(2″-*O*-rhamnosylglucoside) **97**, luteolin-8-C-(2″-rhamnosylglucoside) [54] **98**.

Similar compounds are also found in *P. americana* with the same aglycones apigenin **63** and luteolin **64** [55], but only luteolin-7-*O*-D-glucoside **86** has been reported as a glycone. It is unlikely that these are the only compounds of

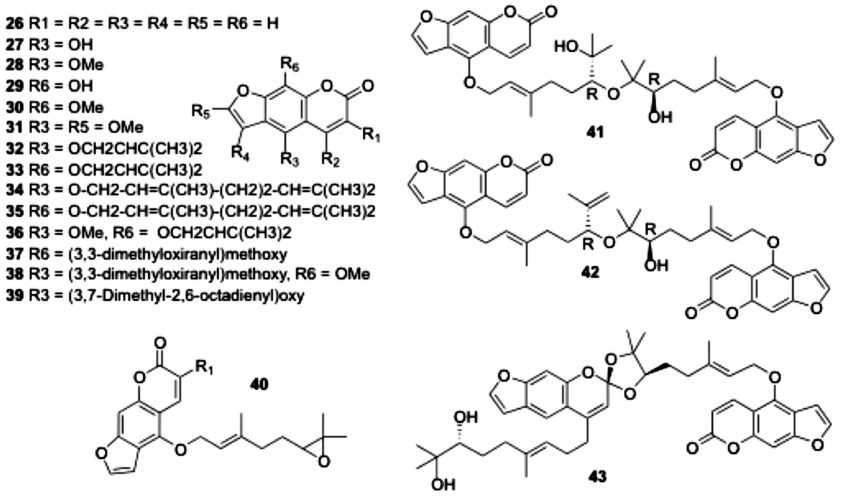


Figure 5. Furanocoumarins.

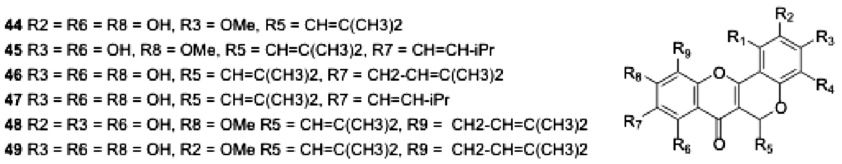


Figure 6. Flavones.

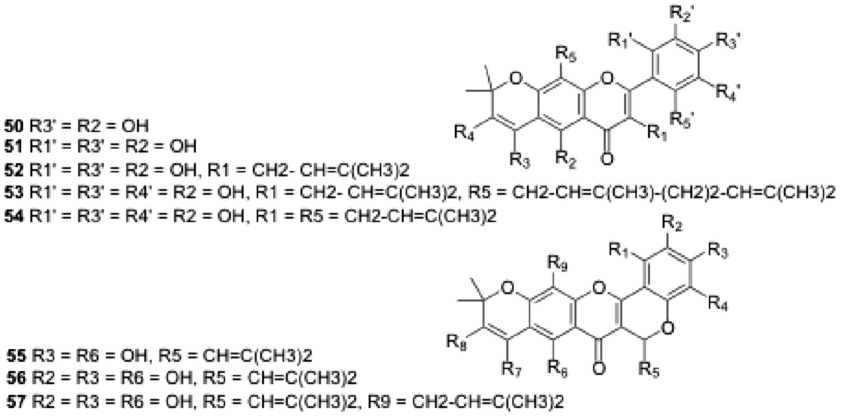


Figure 7. Flavones cont.

this type, and it should be anticipated that more of such derivatives are present in tropical fruit plants in general.

2.3.3 Flavonols

Flavonols (Fig. 10) or 3-hydroxyflavones and O-glucoside forms have also been studied. This subfamily is particularly important due to quercetin **101** and kaempferol **102**, two major flavonols and derivatives that are present in many plant species. For example in *P. americana*, the quercetin derivatives [55], 3-*O*-α-arabinopyranoside **103**, 3-*O*-α-rhamnopyranoside quercitrin **104**, 3-*O*-β-galactopyranoside **105**, as well as isoquercetrin **106**, kaempferol derivatives 3-*O*-α-arabinopyranoside **107**, 3-*O*-α-rhamnopyranoside **108**, 3-*O*-β-D-glucoside **109** also known as astragalin [56], have been isolated and identified.

Similar compounds have been found in *M. indica* with the following quercetin derivatives identified [28, 57, 58]: 3-*O*-arabinopyranoside **103**, 3-*O*-rhamnoside **104** 3-*O*-glucoside **109**, 3-*O*-galactoside **110**, 3-*O*-xyloside **111**, 3-*O*-arabinofuranoside **112**, 3-*O*-arabino-glucoside **113** as well as kaempferol-3-*O*-glucoside **109**. One other flavonol subfamily that has been identified from mango is rhamnetin **114** [59, 60] with 3-*O*-β-galactopyranoside **115** and 3-*O*-β-glucopyranoside **116** derivatives.

D. kaki has been screened for flavonols [61–63], and compounds from the same families have been found. Kaempferol **102** and derivatives, 3-*O*-α-L-arabinopyranoside **107**, 3-*O*-β-D-glucopyranoside **109**, 3-*O*-β-D-galactopyranoside

117, 3-*O*-α-L-rhamnopyranoside **118**, 3-*O*-β-D-xylopyranoside **119**, 3-*O*-(2″-*O*-galloyl)-β-D-glucopyranoside **120** and quercetin **101** and derivatives 3-*O*-α-L-arabinopyranoside **103**, 3-*O*-β-D-galactopyranoside **105**, 3-*O*-β-D-glucopyranoside **106**, 3-*O*-(2″-*O*-galloyl)-β-D-glucopyranoside **121** and isoquercetrin **106**, have all been identified. More recently some of these compounds have been identified in fruit. Thus, quercetin-3-*O*-galactoside **105**, quercetin-3-*O*-glucoside **106** were confirmed and quercetin 3-*O*-rutinoside **113** completed the list. They were all detected in trace amounts [27]. The first two have also been reported in leaves after NMR and MS analysis, along with kaempferol-3-*O*-β-D-glucoside **109**, kaempferol-3-*O*-(2″-*O*-galloyl-β-D-glucoside) **120** and quercetin-3-*O*-(2″-*O*-galloyl-β-D-glucoside) **121** [64]. A specific flavonol subfamily has been discovered with myricetin 3-*O*-β-D-glucopyranoside **123** (Fig. 11) [65].

P. guajava also contains quercetin and the following derivatives: 3-β-galactoside **105**, 3-β-D-glucoside **106** 3-α-L-arabinofuranoside **112** and 3-*O*-rutinoside **113**, as well as kaempferol-3-*O*-glucoside **109** [26].

Quercetin-3-rutinoside **113** has also been found in lychee [66] although no other flavonol has been reported so far in this fruit. No recent identification or studies of flavonols have been reported for the *Musa* genus.

Few reports of *P. edulis* flavonols are available, with mainly the aglycone forms of quercetin **101** and kaempferol **102** being identified [21].

Finally, morin **124** (Fig. 11) flavonol has been identified in species of the *Artocarpus* genus [48]. According to the large number of monosaccharide forms of quercetin and kaempferol, it would be expected that more derivatives of the rhamnetin, myricetin, and the morin family would be found throughout the (tropical) plant kingdom.

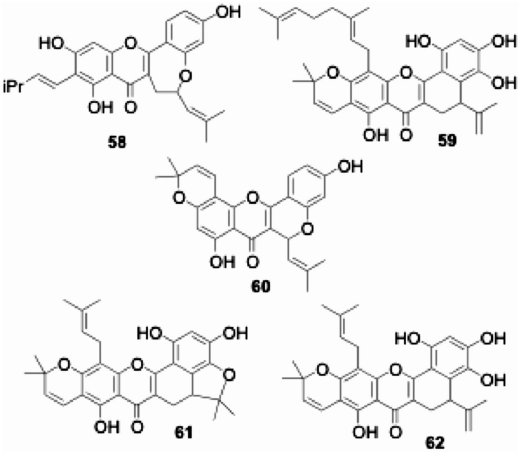
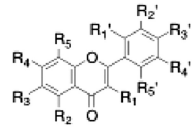


Figure 8. Flavones cont.



63 R3' = R2 = R4 = OH
64 R2' = R3' = R2 = R4 = OH
65 R1' = R3' = R2 = R4 = OH
66 R1' = R3' = R1 = R2 = R4 = OH
67 R1' = R3' = R2 = OH, R4 = OMe
68 R3' = R1 = R2 = R3 = R4 = R5 = OMe
69 R2 ' = R3' = R2 = R3 = R4 = OMe
70 R2' = R3' = R2 = R4 = R5 = OMe
71 R2 = OH, R1' = R4' = R1 = R4 = R5 = OMe
72 R2' = R3' = R1 = R2 = R3 = R4 = R5 = OH
73 R1' = R3' = R2 = R4 = OH, R3 = CH=CH-*i*Pr
74 R1' = R3' = R2 = R4 = OH, R3 = CH2-CH=C(CH3)2
75 R1' = R3' = R2 = R4 = OH, R1 = CH2-CH=C(CH3)2
76 R3' = R2 = R4 = OH, R3 = CH2-CH=C(CH3)2
77 R1' = R3' = R2 = R4 = OH, R1 = CH2-CH=C(CH3)2
78 R1' = R3' = R2 = R4 = OH, R1 = R3 = CH2-CH=C(CH3)2
79 R1' = R3' = R2 = R4 = OH, R1 = CH2-CH=C(CH3)2, R3 = CH=CH-*i*Pr
80 R1' = R3' = R2 = OH, R4 = OMe, R1 = CH2-CH=C(CH3)2, R3 = CH=CH-*i*Pr
81 R1' = R3' = OMe, R4' = R2 = R4 = OH, R1 = R3 = CH2-CH=C(CH3)2
82 R3' = R2 = R4 = OH, R3 = Glu
83 R3' = R2 = R4 = OH, R5 = Glu
84 R2' = R3' = R2 = R4 = OH, R3 = Glu
85 R2' = R3' = R2 = R4 = OH, R5 = Glu
86 R2' = R3' = R2 = OH, R4 = O-Glu
87 R3' = R2 = OH, R4 = OMe, R3 = Glu
88 R3' = R2 = R4 = OH, R3 = R5 = Glu
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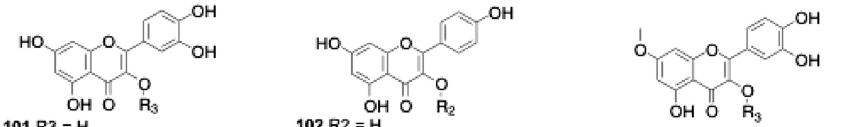
94 R2 = R4 = OH, R3 = R5 = Glu
95 R3' = R2 = R4 = OH, R3 = Glu-Glu
96 R2' = R3' = R2 = R4 = OH, R3 = Glu-Glu
97 R2' = R3' = R2 = R4 = OH, R5 = Glu-Man
98 R2' = R3' = R2 = OH, R4 = O-Glu-Man
99 R3' = R2 = OH, R4 = OMe, R3 = Glu-Glu
100 R3' = R2 = R4 = OH, R2' = OMe, R3 = Glu-Glu

Figure 9. Flavones cont.



101 R3 = H
103 R3 = a-L-Arabinopyranoside
104 R3 = a-L-Rhamnopyranoside
105 R3 = b-D-Galactopyranoside
106 R3 = b-D-Glucopyranoside
110 R3 = a-L-Galactopyranoside
111 R3 = Xyloside
112 R3 = a-L-Arabinofuranoside
113 R3 = arabino-glucoside
121 R3 = (2-O-galloyl)-b-D-glucopyranoside
122 R3 = rhamnosyl-glucoside

102 R2 = H
107 R2 = a-L-Arabinopyranoside
108 R2 = a-L-Rhamnopyranoside
109 R2 = b-D-Glucopyranoside
117 R2 = b-D-Galactopyranoside
118 R2 = a-L-Rhamnopyranoside
119 R2 = b-D-Xylopyranoside
120 R2 = (2-O-galloyl)-b-D-glucopyranoside

114 R3 = H
115 R3 = b-Galactopyranoside
116 R3 = b-Glucopyranoside

Figure 10. Flavonols.

2.3.4 Flavanones

Flavanones (Fig. 12) or 2,3-dihydro-2-phenylchromen-4-ones are less commonly occurring compounds. However, a large variety of these compounds have been reported in tropical fruit plants. In *Artocarpus*, two main families have been recorded: artocarpanone **125** [47] as well as the heteroflavanones A **126**, B **127**, and C **128**. Dihydromorin **129** has also been reported. In citrus, a more diverse set of flavanones [36, 67] have been reported, including naringenin **130**, narirutin **131**, eriocitrin **132**, eriodictyol-7-*O*-rhamnoside **133**, hesperidin **134**, naringin **135**, neohesperidin **136** and neoeriocitrin **137**.

2.3.5 Flavanols

A few flavanols (Fig. 13) (2-phenyl-3,4-dihydro-2*H*-chromen-3-ol) and proanthocyanidins, which are oligomers or polymers of these flavanols, have been found in a selected range of tropical fruits. Principally catechins have been identified, such as (+)-catechin **138** (*P. americana* [68], *Musa* spp. [69], *M. indica* [70] and *D. kaki* [27]), (−)-epicatechin **139** (*P. americana* [68], *D. longan* [71, 72], *L. chinensis* [73], *M. indica* [70], *G. mangostana* [74] and *D. kaki* [27, 75]), (+)-gallocatechin **140**, is reported in *P. guajava* [76], *G. mangostana* [77], *M. indica* [70], and Cavendish bananas [78], while epigallocatechin **141** has been identified in *G. mangostana*, *D. kaki* [75], and *M. indica* [70].

Gallate esters of those catechins are found where the initial catechin was identified. The occurrence of catechins in plants would suggest a much more widespread distribution of this family and thus one would expect to find such compounds in most fruits and vegetables, of both tropical and temperate origin. Leucocyanidin **142** has been found in both *Musa* species [79] and *P. guajava* [19]. *G. mangostana* has been found to contain (+)-afzelechin **143** and epiafzelechin **144** as additional flavanols [77]. Very few proanthocyanidins (Fig. 14) have been found in tropical fruits, with only *D. longan* [80] and *L. chinensis* [73] reported to contain both proanthocyanidin A2 **145** and B4 **146**. Proanthocyanidin content has been reported for a list of tropical fruits but details of the actual structures or identifications of such proanthocyanidins [81] was not provided.

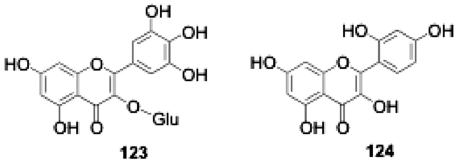
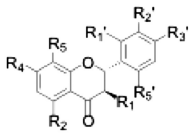


Figure 11. Myricetin 3-*O*-β-D-glucopyranoside and Morin.



125 R1 = R5 = H, R2 = R1' = R3' = OH, R4 = OMe
126 R1 = R5 = H, R2 = OH, R4 = R1' = R3' = R5' = OMe
127 R1 = H, R2 = OH, R4 = R1' = R3' = R5' = OMe, R5 = CH2-CH=C(CH3)2
128 R1 = H, R2 = R4 = OH, R1' = R3' = R5' = OMe, R5 = CH2-CH=C(CH3)2
129 R5 = H, R1 = R2 = R4 = R1' = R3' = OH
130 R1 = R5 = H, R2 = R3' = OH, R4 = O-Man
131 R1 = R5 = H, R2 = R3' = OH, R4 = O-Rut
132 R1 = R5 = H, R2 = R2' = R3' = OH, R4 = O-Rut
133 R1 = R5 = H, R2 = R2' = R3' = OH, R4 = O-Rha
134 R1 = R5 = H, R2 = R2' = OH, R3' = OMe, R4 = O-Rut
135 R1 = R5 = H, R2 = R3' = OH, R4 = O-Rha-Glu
136 R1 = R5 = H, R2 = R2' = OH, R3' = OMe, R4 = O-Rha-Glu
137 R1 = R5 = H, R2 = R2' = R3' = OH, R3' = OMe, R4 = O-Rha-Glu

Figure 12. Flavanones.

2.3.6 Isoflavones

Isoflavone (Fig. 15) occurrence in tropical fruits has not been extensively studied with the exceptions being *P. americana*, *Musa* species, *L. chinensis*, *M. indica*, *C. papaya*, *P. edulis*, *D. kaki* and *A. comosus*, which have all been screened for the presence of specific isoflavones. Daidzein **147**, formononetin **148** and glycitein **149** have been found in all studied species except for papaya. Genistein **150** and and biochanin A **151** have been found in all species examined except in *Musa* [31, 32]. *Artocarpus* plants are the only reported source of artocarpetin A **152** [44].

2.3.7 Anthocyanins

Anthocyanins (Fig. 16) and anthocyanidins (glycosides forms) are charged compounds based on the flavylium cation. They are plant pigments often responsible for the

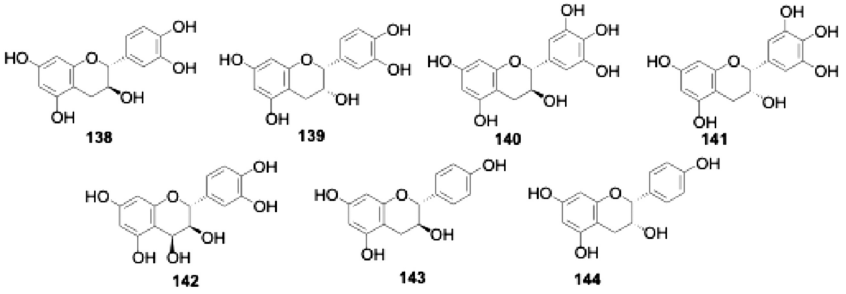


Figure 13. Flavanols.

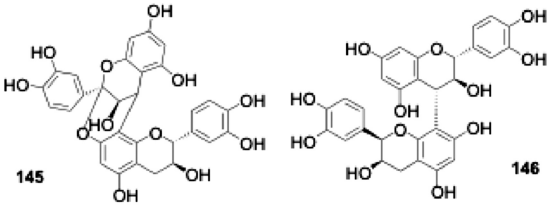


Figure 14. Proanthocyanidins.

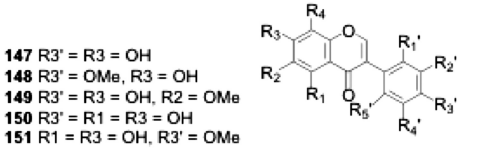


Figure 15. Isoflavones.

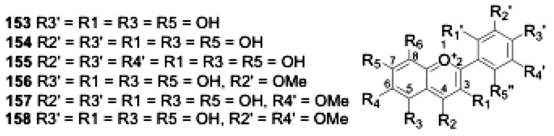


Figure 16. Anthocyanins.

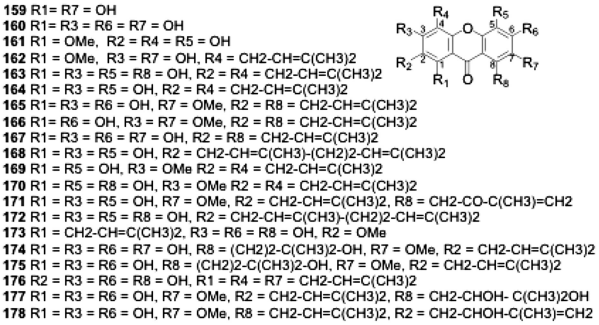


Figure 17. Xanthones.

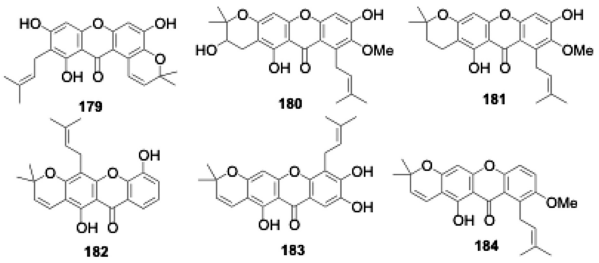


Figure 18. Xanthones cont.

bluish to reddish color typically found in grapes or berries. Although a large number of anthocyanins exist, only the following compounds have been reported in tropical fruits: pelargonidin **153**, cyanidin **154**, delphinidin **155**, peonidin **156**, petunidin **157** and malvidin **158**. *Musa* species for example contain only the rutinoside glycoside form of anthocyanins [82]: delphinidin-3-rutinoside, cyanidin-3-rutinoside, petunidin-3-rutinoside, pelargonidin-3-rutinoside, peonidin-3-rutinoside and malvidin-3-rutinoside. In comparison, lychee fruit contain cyanidin-3-rutinoside and cyanidin-3-*O*-glucoside [66], cyanidin 3,5-diglucoside, cyanidin 3-glucoside, cyanidin 3-rutinoside, cyanidin 3-, pelargonidin 3,7-diglucoside and malvidin 3-acetylglucoside [66]. *P. edulis* also contains mainly cyanidin monosaccharides [21] with cyanidin-3-*O*-glucoside and cyanidin-3-*O*-β-galactopyranoside being reported, but also pelargonidin-3-*O*-glucoside. *D. kaki* leaves have recently been reported containing cyanidin-3-*O*-glucoside [64]. Finally, *M. indica* contains only 7-*O*-methylcyanidin 3-*O*-β-D-galactopyranoside [70]. Other anthocyanins have been tentatively identified from mango but structures have not been confirmed [59].

2.3.8 Xanthones

Xanthones (Fig. 17–19) are a class of secondary metabolites principally found in mangosteen that have attracted strong interest. Their structures are extremely diverse. The following is a list of xanthones identified from different parts of the plant [83–89]: euxanthone **159**, norathyriol **160**, BR-xanthone B **161**, mangosharin **162**, gartanin **163**, 8-deoxygartanin **164**, α-mangostin **165**, β-mangostin **166** and γ-mangostin **167**, mangostinone **168**, cudraxanthone G **169**, 8-hyroxycudraxanthone G **170**, mangostingone **171**, smeaxanthone A **172**, dulxanthone D **173**, garcinone C **174**, D **175** and E **176** mangostenone E **177** and mangostenol **178**. The garcinone A structure has yet to be formally defined.

Garcinone B **179** has a more complex structure resulting from the cyclization of isoprenoid substituents with adjacent hydroxyl functions. These cyclizations can result in linear structures mangostanol **180**, 3-isomangostin **181**, trapezifolixanthone **182**, caloxanthone A **183**, calabaxanthone **184**, demethyl-calabaxanthone **185**, macluraxanthone **186** or garcimangosone A **187** as a pentacyclic compound. Angular structures can also result from cyclization as with 1-isomangostin **188**, 11-hydroxy-1-isomangostin **189**, tovophyllin A **190**, garcimangosone C **191**, mangostenone D **192**. Finally, pentacyclic structures can occur and include the angular xanthones garcimangosone B **193**, BR-xanthone A **194**, mangostenone A **195** and B **196** and tovophyllin B **197**. Furano heterocyclic compounds are also reported with mangoxanthone **198**, mangostenone C **199**, mangostanin **200**, 6-deoxy-7-demethylmangostanin **201** and 6-*O*-methylmangostanin **202**.

Most of these compounds have been reviewed including medicinal properties of the fruit itself [20]. Only one xanthone has been identified so far in the *Artocarpus* genus, artomunoxanthone **196** [47]. Finally, *M. indica* contains an important pharmacological xanthone [70], mangiferin **197** and its derivatives mangiferin gallate **198**, isomangiferin **199**

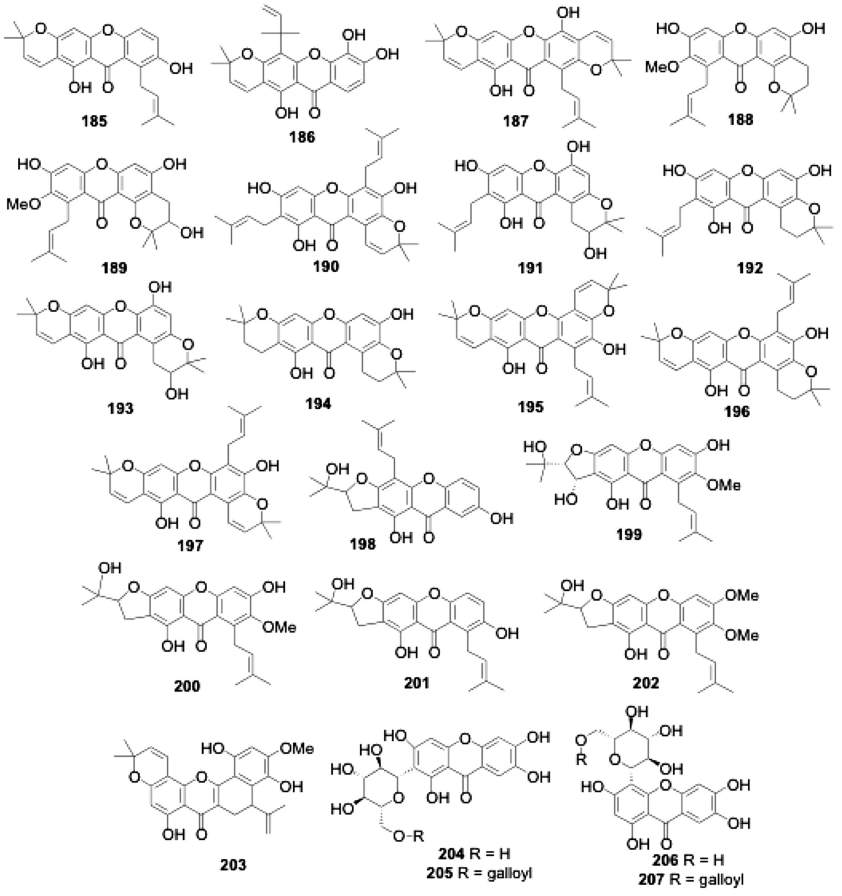


Figure 19. Xanthones cont.

and isomangiferin gallate **200**. As described later in this review, this xanthone has attracted much attention.

2.3.9 Stilbenes

Stilbenes (Fig. 20) are a minor class of polyphenols found in tropical fruits. Although some stilbenes from non-tropical fruits have shown important bioactivity, none from tropical fruits are reported as possible bioactive compounds. Only plants from the *Artocarpus* genus have been found to contain the following stilbenes [45, 90, 91]: oxyresveratrol **208**, artoindonesianin F **209** and *trans*-4-iso-pentenyl-3,5,2′,4′-tetrahydroxystilbene **210**.

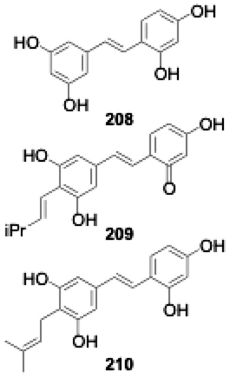


Figure 20. Stilbenes.

2.3.10 Carotenoids

Carotenoids (Fig. 21–23) are tetraterpenoids found throughout the flowering plant kingdom as a pigment mostly responsible for the red, orange or yellow color of fruits. They play a vital role at the core of the photosynthetic reaction center. They are based on a long unsaturated hydrocarbon chain built from isoprene units. Some carotenoids are functionalized along their chain with alcohols, glycosides, ethers or epoxides to form a large family of derivatives. As they are found widely in plants, it is not surprising that a large number of carotenoids have been reported in tropical fruit species.

Carotenoids have been identified by Setiawan et al. [92] and Breithaupt [93] in different fruits through screening for specific compounds. This may explain why several tropical fruits that are reported to contain carotenoids apparently

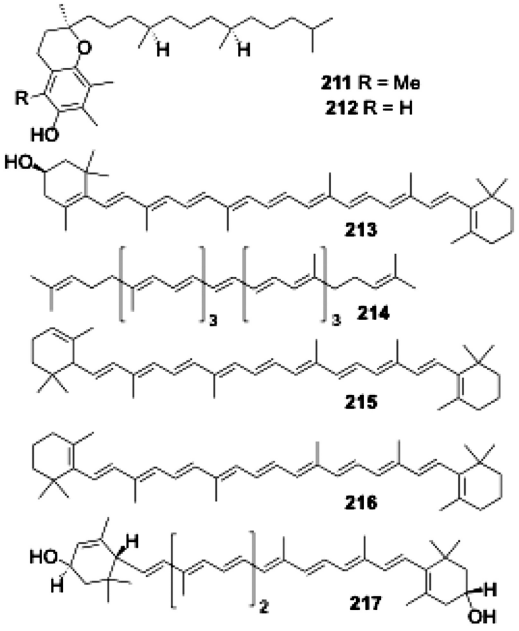


Figure 21. Carotenoids.

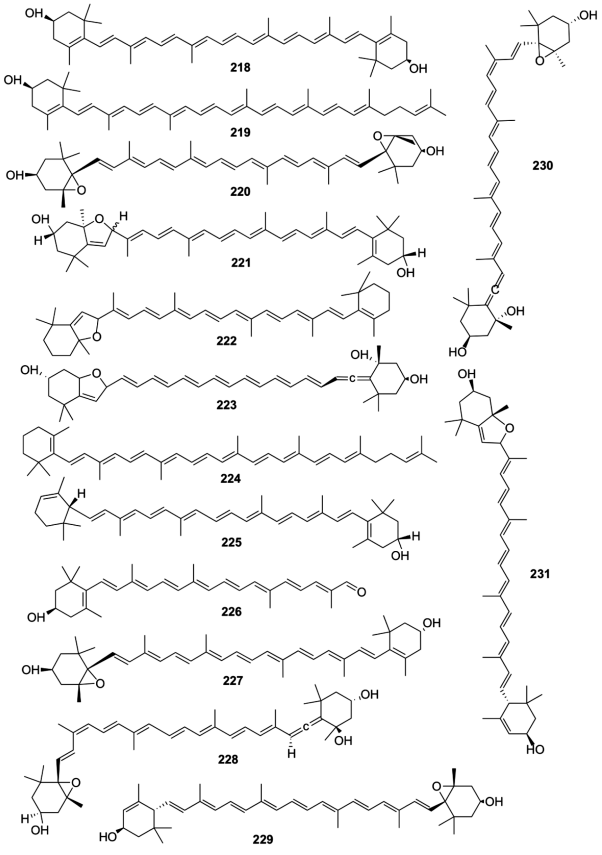


Figure 22. Carotenoids cont.

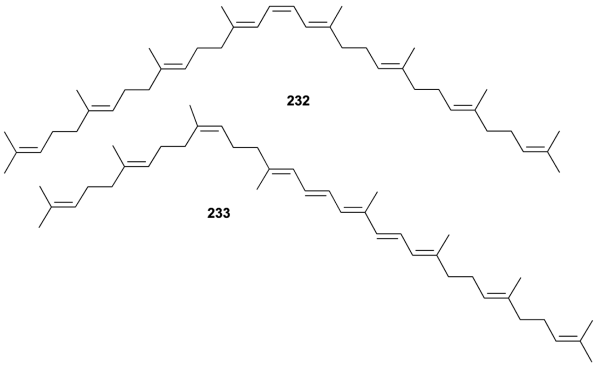


Figure 23. Carotenoids cont.

have less diversity in carotenoid structure than might have been anticipated. It would be surprising if the reported compounds are the only ones present. The currently identified carotenoids from tropical fruit plants are listed below from Setiawan et al. [92] and Breithaupt et al. [93] augmented with more recent reports.

In *P. americana*, α-tocopherol **211** and γ-tocopherol **212**, β-cryptoxanthin **213**, α-carotene **215**, β-carotene **216**, lutein **217** and zeaxanthin **218**. This list can be extended with, violaxanthin **220**, neochrome **223**, neoxanthin **228**, 9″-*cis*-neoxanthin **229**, lutein-5,6-epoxide **230**, chrysanthemaxanthin **231** [94].

In the *Musa* genus, β-cryptoxanthin **213**, α-carotene **215**, β-carotene **216** and lutein **217**. The last three were confirmed in a more recent study [95].

In *P. guajava*, β-cryptoxanthin **213**, β-carotene **216**, lutein **217**, rubixanthin **219** and neochrome **223**.

In *M. indica*, β-cryptoxanthin **213**, lycopene **214**, β-carotene **216** and violaxanthin **220**.

In *G. mangostana*, β-cryptoxanthin **213**, lycopene **214** and β-carotene **216**.

In *C. papaya*, α-tocopherol **211**, β-cryptoxanthin **213**, lycopene **214**, β-carotene **216** and violaxanthin **220**. Recently, β-cryptoxanthin **213**, lycopene **214** and β-carotene **216** were confirmed as the most abundant in the fruit flesh of the maradol cultivar [29].

In *D. kaki*, lycopene **214**, α-carotene **215**, β-carotene **216**, γ-carotene **224**, zeaxanthin **218**, mutatoxanthin **221** and α-cryptoxanthin **225** [61]. A recent study confirms the presence of α-carotene **215**, β-carotene **216**, zeaxanthin **218**, and lists β-cryptoxanthin **213** as a new carotenoid for persimmon [27].

In *A. comosus*, β-cryptoxanthin **213**, lycopene **214** and β-carotene **216**.

P. edulis has been investigated more thoroughly for carotenoids and the following have been identified [21]: β-cryptoxanthin **213**, α-carotene **215**, β-carotene **216**, zeaxanthin **218**, violaxanthin **220**, citroxanthin **222**, γ-carotene **224**, α-cryptoxanthin **225**, β-citraurin **226**, antheraxanthin **227**, neoxanthin **228**, phytoene **232** and phytofluene **233**.

In *Artocarpus heterophyllus*, a recent and very detailed study also suggests more advanced structural composition of the carotenoids from fruits, with isomers of previously listed carotenoids [96] being reported. As these authors judiciously suggest, the characterization of carotenoids requires UV–visible spectrum analysis, spectral fine structure and peak cis intensity to correctly and conclusively attribute identity to carotenoids according to the chromophore suggested. Indeed, the general literature is not as descriptive as their results suggest.

2.3.11 Tannins

Another family of bioactive compounds that have attracted interest is the tannins. This family can be divided into three subfamilies: hydrolyzable tannins, condensed tannins and pseudo-tannins. Hydrolyzable tannins are reported in this section, whereas condensed tannins are more complex polyphenols that are classified more generally in the proanthocyanidin group. Pseudotannins comprise the lowest molecular weight tannins and are usually of simpler structure. The general structure of hydrolyzable tannins is reported for tannic acid (Fig. 24) (deca-galloyl-glucose) **234**.

M. indica also contains some hydrolyzable tannins such as tetragalloyl-glucose [97], pentagalloyl-glucose and hexagalloyl-glucose, or more complex compounds but with undefined fine structure, such as heptagalloyl-glucose and octa-galloyl-glucose and nonagalloyl-glucose [58].

Due to the relatively simple structures of such tannins, it is surprising that they have not been reported in more tropical fruit species. It would be anticipated that this family of compounds would be ubiquitously present in the flowering plants, and their not being reported is probably due to a lack of appropriate screening for such compounds rather than their absence.

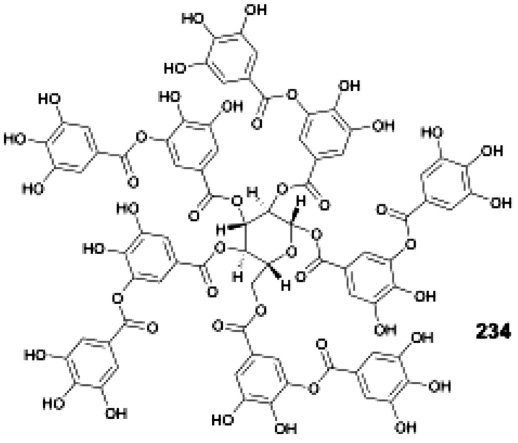


Figure 24. Tannic acid.

2.4 Unusual families of compounds isolated from tropical fruits

While polyphenols, phenolic acids and carotenoids are ubiquitously found in flowering plants, some less common subclasses are sometimes reported in certain fruits.

Acetogenins (Fig. 25) are polyketides found in plants, fungi, bacteria and in animals with specific biosynthesis pathways for each origin. Acetogenins like annonacin **235** or uvaracin **236** are specifically found in the *Annona* genus of the Annonaceae plant family [98–103], although some reports mention acetogenins in *Rollinia mucosa* [104, 105]. Biogenetically they are derived from the polyketide biosynthesis pathway involving polyketide synthases. More than 400 annonaceous acetogenins have been reported and they display mainly cytotoxic and anti-tumor activity, with a potent multidrug-resistant anti-tumor effect. More diverse activities are also reported, including anti-bacterial, parasiticidal and pesticidal activity.

Kauranes (Fig. 26) **237**, which are diterpenoid derivatives (four isoprene units), are also reported specifically in *Annonaceae* plants [106, 107], whereas triterpenoids (six isoprene units) are more common among tropical fruit plants.

P. guajava contains a number of triterpenoids (Figs. 27–29) [108–110], mostly from the ursolic acid **238** derivative family including oleanolic acid **239**, uvaol **240**, goreishic acid I **241**, corosolic acid **242**, guavanoic acid **243**, neriucoumaric acid **244**, isoneriucoumaric acid **245**, ilelatifol D **246**, guavacoumaric acid **247**, guajavolide **248**, guavenoic acid **249**, asiatic acid **250**, obtusinin **251**, jacoumaric acid **252** and β-sitosterol **253**. Most of these compounds have been identified through advanced methods such as NMR (^{1}H and ^{13}C) and mass spectrometry.

P. edulis [21] contains the steroidal triterpenoid passiflorine **254** [111]. Interestingly, this compound has not been

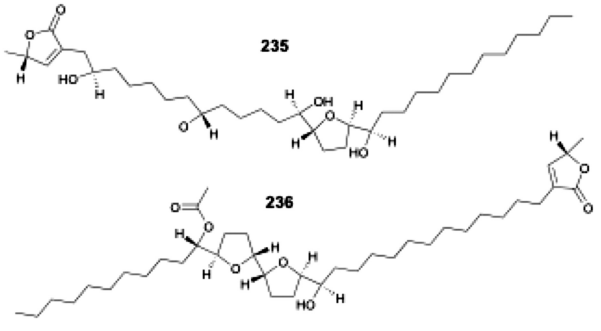


Figure 25. Acetogenins.

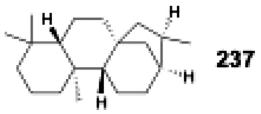


Figure 26. Kauranes.

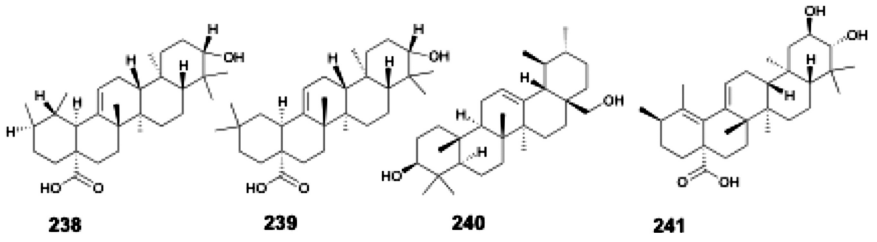


Figure 27. Other triterpenoids.

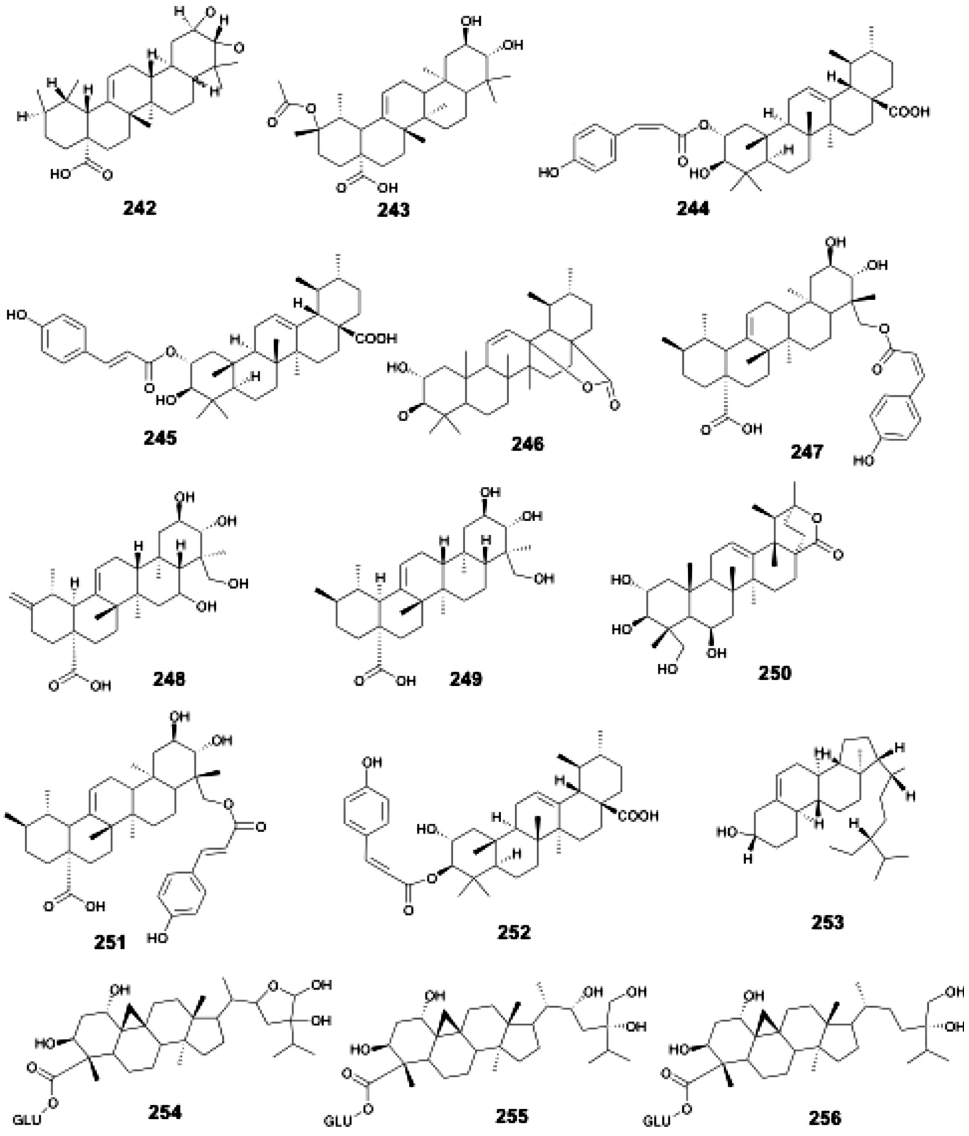


Figure 28. Other triterpenoids cont.

widely reported. Additional derivatives have also been isolated and identified as cyclopassiflosides I **255**, II **256**, III **257**, IV **258**, V **259** and VI **260**, as well as the cylopassifloic acids A **261**, B **262**, C **263** and D **264**. All of these compounds have been characterized by ^{1}H and ^{13}C NMR and fast atom bombardment mass spectrometry (FABMS).

In addition to the triterpenoids, another subfamily has been isolated and identified from the passionfruit that belongs to the alkaloid pyridoindole family [112]. These compounds are harman **265**, harmine **266**, harmaline **267** and harmalol **268**.

D. kaki [61] contains some di- and triterpenoids including ursolic acid **238**, oleanolic acid **239**, uvaol **240**, lupeol **269**, α-amyrin **270**, pomolic acid **271**, taraxerol **272**, β-sitosterol **253**, β-sitosterol glucoside **273**, stigmasterol **274**, campesterol **275**, and also compounds of the triterpenoid subfamily

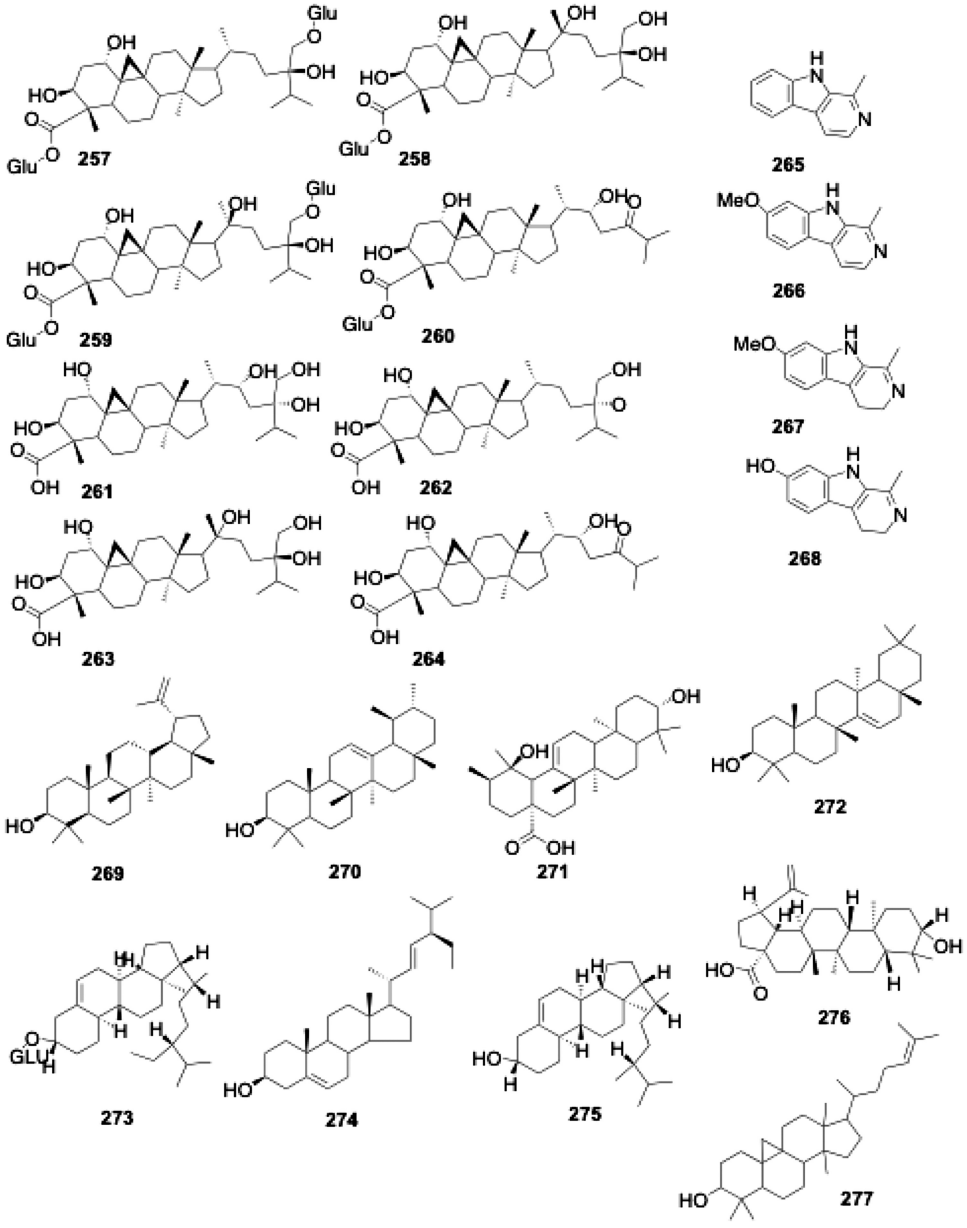


Figure 29. Other triterpenoids cont.

named betulinic acid **276** and its derivatives. Along with *D. kaki*, *A. heterophyllus* is the second fruit of this reviewed list that contains ursolic acid **238**, β-sitosterol **253**, betulinc acid **276** and cycloartenol **277**, as reviewed recently [113].

D. kaki is the only tropical fruit plant in this review that has been reported to contain naphthoquinones (Fig. 30). Derivatives include plumbalgin **278**, 7-methyljuglone **279**, shinanolone **280**, 3-methoxy-7-methyljuglone **281**, diospyrin **282**, isodiospyrin **283**, neodiospyrin **284**, maritinone **285**, mamegakinone **286**, as characterized by NMR, MS, UV and IR from *D. kaki* [61] and plumbalgin **268**. Although shinanolone, as reduced 7-methyljuglone, has been reported in *D. kaki*, the reduced product of plumbalgin (iso-shinanolone) has not been reported in this species, but in other *Diospyros* species. The fully reduced product has not yet been isolated from any species of the genus [61]. More compounds of the naphthalene family have been reported from the heartwood of the *D. kaki* tree. They are 4-hydroxy-5,6-dimethoxy-2-naphthaldehyde **287**, 5,6,8-trimethoxy-3-methyl-1-naphthol **288** and 4,8-dihydroxy-5-methoxy-2-naphthaldehyde **289**, in addition to two previously reported 2-naphthaldehydes: 4-hydroxy-5,8-dimethoxy-2-naphthaldehyde **290** and 4-hydroxy-5-methoxy-2-naphthaldehyde **291** [114, 115].

The last family of less commonly observed compounds reviewed here is the cyclopentene carbonitriles (Fig. 31). Only *P. edulis* is reported to contain these [21], in particular passicapsin **292**, passibiflorin **293**, passicoriacin and its epimers epipassicoriacin, and epitetraphyllin B **294**.

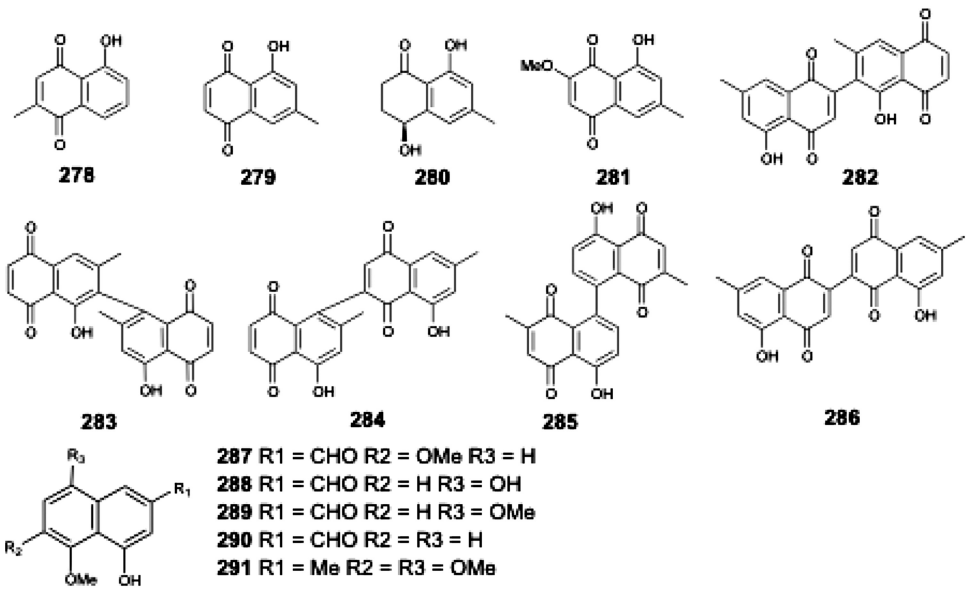


Figure 30. Naphtoquinones.

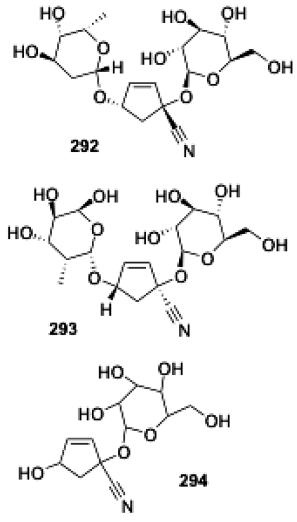


Figure 31. Cyclopentene carbonitriles.

As observed throughout this listing of bioactive molecules, the natural product families found in tropical fruit plants are ubiquitously observed in all fruit plants, whether temperate or tropical. The uniqueness of tropical fruits, typically recognized through the flavors and appearance of the fruits, is almost certainly due to a complex combination of such compounds. The presence of a unique compound family limited to one specific fruit plant may indicate biosynthetic pathways specific to this family. But as a general observation, families of compounds present in plants are not specific to the geographic area where the plant grows. This indicates that general biosynthesis pathways for flavonoids are generally used throughout the whole flowering plant kingdom. Tropical fruits are no exception to this observation as we report here the presence of bioactive compounds found in many other plants. But the mixture of compounds present in one fruit may make it more suited to cure certain ailments than another, as recorded in the folk medicinal usage.

3 Tropical fruit plants with known bioactivities

The bioactivities of tropical fruit plants are reported in this section in association with a description of each fruit. Although isolated compounds have been studied for a range of bioactivities, in the context of fruit consumption, it is more relevant to consider extracts rather than isolated compounds. Indeed, due to the variety of bioactive compounds they contain, the synergy of compounds within a plant extract is likely to be important. Furthermore, it is generally observed that extracts containing a mixture of natural bioactive compounds can have a stronger effect on a specific health status than individual compounds present in the fruit [116].

Due to the polyphenolic nature of many compounds, anti-oxidant activity has been reported for all tropical fruits reviewed here. Anti-oxidant activity and total phenolic content have been determined using various methods and techniques, including the Folin-Ciocalteu assay, ferric reducing anti-oxidant power (FRAP), oxygen radical absorbance capacity (ORAC), 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging activity, (Trolox)-equivalent anti-oxidant capacity (TEAC), 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) anti-oxidant assay, ferric thiocyanate (FTC), total reactive anti-oxidant potential (TRAP) and ascorbic acid content (AAC). The anti-oxidant activity of all reviewed tropical fruits was determined with one or more of these methods, but as this is not a direct indicator of

nutritional potential, anti-oxidant activity will not be reviewed further for each individual fruit plant.

In the following sections, information about the nature and pharmacological properties of 13 tropical fruit families consumed in Australia are described. The molecular structures of individual molecules identified in this section have been detailed previously. The description of fruits was listed according to the methodology employed by Queensland Department of Primary Industries and Fisheries [117, 118].

3.1 Annonaceae family

Annonaceae family also called ''custard apple family'' from the *Magnoliales* order contains more than 2300 species within four genera that include species producing edible fruits. They are native to the tropical regions of the world. The *Annona* genus is the second largest genus of the family with seven species including custard apple and sugar apple, cherimoya and soursop, which are cultivated for domestic or commercial use, mostly for their nutritious fruits. The green-skinned fruits are oval to spherical, consist of many white fleshy fibrous subparts called syncarps, each containing one bean-like seed with a toxic kernel [117, 118].

Plant extracts from Annonaceae family members have been particularly studied in the last ten years. An early study reported their cardiotonic activity [119]. Soursop (*Annona muricata*) has been studied for anti-HSV-1 (herpes simplex virus 1) activity showing a total cytopathic effect inhibition at 1 mg/mL [120]. Sugar apples (*Annona squamosa*) yielded positive hypoglycemic effects on alloxan-induced diabetic rabbits. Feeding fruit pulp to rabbits gave a general benefit at a nutritional level as well as a hypoglycemic effect [121]. In related effects on alloxan-induced diabetic Wistar male rats, aqueous leaf extracts showed anti-lipidemic and anti-diabetic effects, possibly due to quercetin-3-*O*-glucoside **109** [122–124]. Cytotoxic activity on HepG2, KB, HCT-8, A549, MCF-7, PC-3, HOS, SK-MEL-2, Caki, KB-VIN, 1A9, PTX10 and U937 tumor cell lines has been associated with annonaceaous acetogenins (cf. Section 2.5) [121, 123, 124]. Although those compounds are not polyphenols, extracts or isolated compounds from this family are known to contain potent cytotoxic bioactive compounds [99]. Liaw et al. showed a pro-apoptotic activity of one of those acetogenins on HepG2 and 1A9 cell lines [98]. Anti-protozoal activity has been suggested against *Leishmania braziliensis*. Despite a fourfold more potent cytotoxicity against U-937 human leukemic cells than the prescribed drug Glucantim (meglumine), the anti-protozoal activity of the ethanolic extract was 40 times more potent against *L. braziliensis* promastigotes [102]. The anti-protozoal and cytotoxic activities have been confirmed with potent activity of extracts from plants of the *Rollinia* genus on both *Leishmania* and *Plasmodium* species [125]. An anti-inflammatory study showed an 80% size reduction of rat paw swelling with custard apple (*Annona reticulata*) seed oil extract at 250 mg/kg [126]. Anti-microbial studies on a series of Gram (+) and Gram (−) bacteria showed a more potent activity of petroleum ether extracts compared with ethanol extracts. This confirms the bioactivity of the acetogenins contained in the *Annonaceae* seeds [127]. *A. squamosa* extracts have been tested among extracts from other plants including *Artocarpus integrifolia*, *P. guajava* and *Averrhoa carambola* for anti-rotavirus activity as part of a comparative study of medicinal plants used in Brazil. *Annonaceae* extract exhibited a modest inhibition of the human rotavirus HCR 3 strain at the maximum non-toxic concentration. *P. guajava* showed a strong inhibition of the SA11 simian rotavirus compared with *Averrhoa carambola* extract which resulted in a modest activity; *Artocarpus integrifolia* extract showed the most potent activity with nearly 100% inhibition against both rotaviruses [128].

3.2 *Artocarpus* genus

Fruit bearing trees of the *Artocarpus* genus belong to the Moraceae family and are native to Southeast Asia and pacific regions. Their fruits are similar to those of the *Annona* in terms of shape and texture. However, the fruits (jackfruit, breadfruit) are generally bigger than custard apples [117, 118].

Potential anti-cancer agents have been found in tissues of breadfruit (*Artocarpus altilis*), with wood extracts exhibiting anti-cancer activity in human breast cancer T47-D cells. These anti-cancer effects may invoke a mechanism involving pro-apoptotic (programmed cell death) effects in part through blocking the sub-G1 phase of the cell cycle [129]. More generally, cytotoxicity has been reported against P-388 rat leukemia cells with an IC_{50} less than 2 μg/mL [42, 91], as well as MCF-7 breast cancer, TK-10 renal cancer and UACC-62 melanoma cells. More detailed studies have been conducted in B16 melanoma cells [48, 49] focused on characterizing the effects of *Artocarpus* sapwood and heartwood bioactive compounds on melanin biosynthesis. Tyrosinase inhibition studies suggested that prenylated flavones identified in jackfruit (*A. heterophyllus*) wood as reviewed in Section 2.3.2, could be potent agents for whitening skin pigmentation [46]. Three prenylated stilbenes from chempedak (*A. integer*) aerial parts have been evaluated for their anti-malarial activity against multidrug-resistant *Plasmodium falciparum* K1, and nine prenylated flavones on chloroquine-sensitive 3D7 strain. Comparatively, heteroflavanone C **128** has shown a very potent activity with detectable activity at 0.414 ng/L on the chloroquine-sensitive strain while the most potent stilbene only exhibited activity at 1.7 mg/L [43, 90]. An extensive study of 15 isolated flavonoids has determined their anti-inflammatory activity in RAW 264.7 cells by assessing the release of chemical mediators (β-glucuronidase, histamine, lysozyme and superoxide anion formation) from mast cells, or by assessing the formation of prostaglandin E2 inducible nitric oxide synthase and cyclo-oxygenase 2 protein expression [45, 47].

3.3 *Persea americana*

Avocado of the *Lauraceae* family is native to the Caribbean, Mexico, South and Central America. It is very popular and cultivated throughout the world in tropical and subtropical regions. The fruit is pear-shaped with a dark green to black-pebbled skin, green to yellow fibrous flesh containing a large seed in its center [117, 118].

Ding et al. reviewed the chemoprevention properties of the avocado fruit, listing the major phytochemicals of *P. americana* and their anti-proliferation effects on cell growth. These authors particularly emphasized the pro-apoptotic effect of avocado extracts [55]. Additional anti-cancer effects were reported on prostate cancer cell lines PC-3 (androgen-independent) and LNCaP (androgen-dependent) [130]. Gallagher et al. reported an anti-hyperglycemic effect in vitro suggesting that avocado fruit could be used as a dietary supplement in type 2 diabetes [131]. Leaf extracts have been studied for their anti-viral (herpes simplex and rabies viruses) activities with an almost total inhibition of HSV-1, and rabies virus strains, because similar extracts have shown virucidal, virustatic, and anti-HIV-1 effects [56, 132, 133]. Analgesic and anti-inflammatory in vivo effects have also been reported for aqueous leaf extracts in Wistar rats and Swiss mice [134]. In this study, anti-inflammatory activity in rodents, as measured by paw oedema size decrease, was most pronounced 3 h after feeding. Analgesic effects were shown to be both central and peripheral. Finally, in vivo hypotensive activity was reported in anaesthetized normotensive rats fed with avocado leaf extracts, by measuring arterial blood pressure [135].

3.4 *Musaceae* family

Banana is an important food crop and staple food for millions of people in developing countries. Worldwide production of bananas in 2007 was more than 85 million metric tons, largely from India and China. Taxonomically, bananas belong to the genus *Musa* of the *Musaceae* family. The majority of edible bananas originate from two wild species, *Musa acuminata* and *M. balbisiana* and their hybrids, and include desert bananas and plantains. The yellow green or red skinned fruit range from a few centimeters to 30 cm long and no more than 10 cm wide, with an oblong cylindrical shape. The fibrous flesh can be white, yellow or salmon pink depending on the genotype [117, 118].

In a short review related to banana (*Musa sapientum* and other species) medicinal properties, Biplab De et al. [136] gave an overview of banana bioactivity studies. The anti-ulcerogenic activity of banana has been known for almost 35 years [137]. It has been suggested that gastro-protective effects include a positive effect on mucosal glycoprotein and cell proliferation [138]. One active ingredient in banana fruit has been identified as the flavanol leucocyanidin **142**, which increased mucus thickness by almost 200% in the case of native leucocyanidin, and by 120% in the case of hydroxylated or tetraallyl leucocyanidin, in aspirin-induced erosions in rats [137]. Ulcer healing and ulcer preventive effects of two banana species (*M. paradisiacal* and *M. sapientum*) have been shown in indomethacin-induced ulcers in rats, but not in acetic acid-induced chronic ulcers [138, 139]. Cell growth regulation was reported by Sun et al. [140] measuring a low anti-proliferative activity of banana on HepG2 cells (EC_{50}, 110 mg/mL). The development and/or progression of malignant ascites in mice given a ripe banana fruit extract diet is suggested as potentially being due to nitric oxide synthesis stimulation [141]. A diet of banana flower extracts at 0.25 g/kg had a significant hypoglycemic effect in the liver and kidney of alloxan-induced diabetic rats compared with non-diabetic and untreated diabetic rats, with the clinically used therapeutic glibenclamide as a positive control [142, 143]. More surprisingly, an anti-clastogenic effect was shown for banana fruit extracts in benzo[*a*]pyrene-induced clastogenicity in bone-marrow cells from male mice, resulting in a strong decrease of micronucleated polychromatic erythrocytes [144]. This was confirmed by Botting et al. [145] who measured the effect of heptane extracts of green banana as a putative anti-mutagenic agent on *Salmonella* strain TA1538.

3.5 *Psidium guajava*

Guava is the fruit of a small tree belonging to the *Psidium* genus of the *Myrtaceae* family. The genus contains about a 100 different species. Cultivated in many tropical and subtropical regions, it is native to Central and northern South America, and Southeast Asia. The fruit is a few centimeters (up to roughly 10 cm) long, oval or round shaped. The skin of unripe fruit turns from green to yellow or maroon when close to maturity, while the flesh color varies from white to deep pink depending on the species [117, 118].

Guava (*P. guajava*) is much studied as a tropical fruit. Interest in this fruit is such that an extensive review was published in 2008 listing the traditional uses, phytochemistry and pharmacology of the plant [19]. In addition to its anti-oxidant properties, the biological activities of guava include the following: anti-diarrheal, anti-microbial, skin infection and wound healing, anti-malarial, anti-tussive, hepatoprotective, anti-genotoxic and anti-mutagenic, anti-allergic, anti-cancer, cardiovascular and hypotensive effects, hypoglycemic, treatment for muscular dystrophy, anti-inflammatory and anti-nociceptive [19]. Guava is a particularly important plant for its anti-hyperglycemic properties. Recent studies suggest that guava represents a new therapeutic lead against human diabetes, as extracts from raw fruit peel resulted in marked hypoglycemic and anti-hyperglycemic activity in normal and streptozotocin-induced diabetic rats [146]. Treating hepatocytes with guava leaf

extracts, Cheng and co-workers observed an uptake of glucose by the cells, suggesting that the hypoglycemic effect of the extract may be a consequence of uptake by hepatocytes [147]. Isolation of active principles from this extract led to the identification of quercetin **101** [147]. However, as this phytochemical is common in the plant kingdom, synergistic effects with other compounds should be considered for the bioactivity of whole extracts from guava leaf. The antimicrobial activity of guava leaves has been compared with that of other plants against fourteen bacterial and fungal strains. *Staphylococcus aureus* and *Candida albicans* were the only microorganisms whose growth was inhibited by guava leaf extracts [148]. More comprehensive studies on *S. aureus* inhibition by guava extract showed a synergistic effect with the following drugs: tetracycline, chloramphenicol, erythromycin, vancomycin, oxacillin, cephalothin, ampicillin, cefoxitin and co-trimoxazole [149]. An anti-thrombotic effect from leaf extracts has been found recently through inhibition of methylglyoxal-induced hypercoagulation [150]. In accordance with folk medicine use of guava, anti-inflammatory, analgesic and anti-pyretic effects of methanol extracts of the leaves have been determined in a range of pharmacological studies reported in the major review cited previously [19]. Similar effects of the extract were found when feeding rats and mice 200 mg/kg of the extract as compared with 150 mg/kg acetylsalicylic acid [151]. In the same study, intestinal motility was measured to assess anti-diarrheal properties. A 50-mg/kg pre-treatment reduced the intestinal travel of a charcoal meal by half compared with control. More interestingly, the leaf extract showed a selective anti-cancer effect on the prostate cancer DU-145 line, as compared with the non-tumorigenic prostate epithelial PZ-HPV-7 cell line [152]. Anti-proliferative effects on the DU-145 cancer cell line were obvious in a dose- and time-dependent manner when using more than 0.5 mg/mL and for 72 h treatment [152]. Further evidence of selectivity is seen in reports suggesting a pro-apoptotic effect of the extract, causing an arrest of 7% of cells in the sub-G1 phase at 0.1 mg/mL increasing up to 36.7% at 1 mg/mL. This effect may be due to caspase-3 expression, which was much higher in DU-145 than in PZ-HPV-7 cells after pre-treatment with the extracts. In the same study, an anti-metastatic effect was also suggested, via down-regulation of MMP-2 and MMP-9 protein expression (key proteases important in metastasis), this effect was seen even at a low concentration of guava extract [153].

3.6 *Citrus* genus

Limes, lemons and pummeloes are examples of fruits of plants in the *Citrus* genus, *Rutaceae* family, cultivated in most tropical and subtropical regions of the world and believed to originate from Southeast Asia [154]. Fruits are mostly round, but size, skin and flesh color vary depending on the species. Limes and pummeloes are green while lemon has bright yellow skin and flesh. Other subtropical species include oranges, clementines and grapefruit, and are mainly hybrid cultivars [117, 118].

Due to the large number of *Citrus* species and hybrid cultivars, pharmacological studies of these plants are very varied and extensive, although only a few pharmacological bioactivities have been reported. It has been suggested that citrus fruit juice–drug interaction may be due to the inhibition of CYP3A by furanocoumarins (cf. compounds **12** and **19**–**32** Section 2.3.1) present in the fruits [41]. CYP2C9 cytochrome inhibition by different citrus fruit juices was also investigated [155]. Using human liver microsomes and the measurement of the residual activity of the cytochrome in hepatic drug metabolism to hydroxylate diclofenac and tolbutamide, when treated with 25 μL (5% v/v) of fruit juice. Among the 18 fruits studied, nine *Citrus* species were investigated. The residual activity on diclofenac hydroxylation was 31% for grapefruit (*Citrus paradisi*), and 42.8% for key lime (*Citrus aurantifolia*). Tolbutamide hydroxylation was much less inhibited. Papaya (*C. papaya*) and pineapple (*A. comosus*) showed a much more pronounced inhibition of the CYP2C9 drug metabolism [155]. This pronounced inhibition may be serious for the metabolism of drugs through the CYP2C9 pathway. Phytophotodermatitis described by Nigg et al. [35] was attributed to coumarins of general structure represented in compound **11** identified in lime peel or juice. Citrus fruit peel is reported to possess anti-inflammatory properties in lipopolysaccharide-activated RAW264.7 cells. Choi et al. [156] showed that a hexamethoxyflavone (cf. Section 2.3.2) present in *Citrus sunki* fruit peel is responsible for the interruption of NF-B DNA-binding activity and the suppression of reactive oxygen species. Huang et al. [157] demonstrated that polymethoxyflavones (cf. Section 2.3.2) contained in citrus fruit peel exerted an inhibitory activity on PGE2 and NO production through transcriptional regulation of COX-2 and iNOS genes. In a screen of 17 *Citrus* species for general pharmacological properties, both anti-corpulence and anti-cancer activities were reported by Hirata et al. [50]. Seventeen *Citrus* species were assessed for oil droplet accumulation in 3T3-L1 pre-adipocytes. In the same study, these species were also assessed by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay on HT29 colon cancer cells with *Citrus canaliculata*, *Citrus tamaruna*, *Citrus kinokuni* and *Citrus tachibana* peel extracts showing anti-proliferative activity ranging the 50 μg/mL [50]. Further anti-cancer studies showed that two compounds from sour orange (*Citrus aurantium*), limonexic acid and sitosterol glucoside, had a specific anti-proliferative effect on HT-29 cells, compared with COS-1 as a non-cancer cell line control, inducing cell arrest in the G2/M phase of the cell cycle [158]. An anti-platelet study of an aqueous alcoholic extract of lime leaves showed that the extract inhibited significantly ADP- or epinephrine-induced platelet aggregation in a concentration-dependent manner with IC50 s of 0.40 and 0.32 mg/mL, respectively [51].

3.7 *Litchi chinensis*

Lychee is the sole member of the *Litchi* genus, *Sapindaceae* family. *L. chinensis* is divided into two subspecies (*L. chinensis chinensis* and *L. chinensis phillipinensis*), based both on origin and botanic characteristics of leaflets. The fruit resembles that of the longan (*D. longan*), but its shell is usually reddish, while its flesh is translucent. The fruit is 3–4 cm and the flesh is similar to that of a grape, but less juicy [117, 118].

Compared with other fruits considered here, lychee has not been particularly well studied in terms of bioactivities. Despite the popularity of this fruit, with Southeast Asian production reaching two million tons [159], few articles regarding its pharmacological use have been published. On the anti-proliferative level, the lychee seed has a weak anti-leukemic effect on both K562 and U937 cells with IC50 s close to 500 μg/mL and a selectivity index of 6 and 5, respectively when compared with the normal lung cell line HEL99. In the same study, mangosteen (*G. mangostana*) rind showed a stronger anti-proliferative effect and a much higher selectivity index [160]. The stimulatory effects of a proanthocyanidin-containing litchi pericarp (cf. flavanol Section 2.3.5) extract on mouse splenocyte proliferation, and on in vitro anti-proliferation assays on human embryonic lung fibroblasts (HELF) resulted in a stronger inhibitory effect on HELF than on MCF-7 cells. Compounds isolated from this extract (epicatechin and proanthocyanidin B2) had lower cytotoxicities than the anti-cancer drug paclitaxel [161]. Oligonol, a flavonoid oligomer (cf. Section 2.3.1), resulted in both an anti-oxidative effect in adipocytes and fat accumulation in HW and HB2 cell lines [162]. The authors of this study suggest that the schematic cascade model induced by flavonoids in adipocytes links the decrease in oxidative stress to a down-regulation of transcriptional activity of NF-KB and phosphorylation of ERKs, leading to an attenuation of dysregulated expression of genes for adipokines, which would lead to beneficial effects against obesity-induced metabolic syndrome [162]. Oligonol from lychee was also assessed for its effect on abdominal obesity in a clinical study on 19 subjects. The results showed a clear reduction of the different body parameters, particularly the waist circumference, and the visceral fat area. The authors also assessed serum content for adiponectin, leptin and resistin, showing an up-regulation of adiponectin while the two others were not affected. This suggests that oligonol may effectively improve insulin resistance and reduce obesity [163]. To complete the activity of litchi extract related to fat metabolism and fat-related pathologies, a recent article explored the protective effect of litchi flower extract in vivo on the cardiovascular health of high-fat fed hamsters [164]. Conclusions from this study indicate that a down-regulation of fatty acid synthase gene, and up-regulation of peroxisome-proliferator-activated receptor α gene contributes to the reduction of lipids content in serum and liver after intake of *L. chinensis* Sonn. Flower extract.

3.8 *Mangifera indica*

Mango (*M. indica*) belongs to the genus *Mangifera* comprising many species of tropical fruit bearing trees of the *Anacardiaceae* family. Originating from India where most of the world production comes from, it is one of the most well-known tropical fruits, widely appreciated for its juicy fibrous flesh. The fruit is variable in size and color depending on the hundreds of existing cultivars [117, 118]. The flesh is usually yellow or orange and contains a large number of phytochemicals. It is for this reason that it is one of the most studied tropical fruit plants, with some proven health-related bioactivities as described below.

Bioactivities reported for mango are mainly related to Vimang®, a commercial source of a natural extract of the mango tree bark. Available in Cuba, its main use is as a nutritional supplement with characterized anti-oxidant properties. Vimang® has been extensively studied [165–177]. A recent review emphasizes the use of this extract to potentially treat neuropathic pain [178]. Studies have also focused on mangiferin, a glucosylated xanthone [175, 179–183], as a main component of Vimang®, of which mango fruit is also a rich source. Masibo and He (2008) have listed the pharmacological properties of mangiferin, ranging from anti-oxidant activity to immunomodulation [70]. Some studies have shown cytoprotective properties, including a few reports of hepatoprotection. Rat liver microsomes have shown a decrease in lipid peroxidation after treatment with a mango extract by measuring thiobarbituric acid absorbance [184]. Hepatoprotective effects are also reported in cultured rat hepatocytes, by measuring the production of malondialdehyde and assessing the reduced gluthathione status in culture media [185, 186]. Thai mango seed kernel extract and individual active compounds from mango, methyl gallate, gallic acid (cf. Section 2.2), and pentagalloylglucopyranose (cf. Section 2.5) were assessed for CCl_4-induced toxicity and for in vitro anti-inflammatory activity by the inhibition of 5-lipoxygenase [187]. The HepG2 cell line was also studied for cytoprotective and anti-genotoxic effects of mangiferin **197** on $CdCl_2$-induced oxidative stress [188]. Additional cytoprotective effects on ethanol- and indomethacin-induced gastric injuries in rodents have been reported [189]. Gastroprotection was also evidenced from anti-ulcerogenic effects in rats, using four different models of gastric lesions, and testing up to 1 g/kg of aqueous decoction [190]. Additional in vivo studies by Sanchez et al. [191] assessed the pharmacological effect of Vimang® in peritoneal macrophages. They showed that the commercial mango tree bark had a stronger effect on tetradecanoylphorbol acetate (TPA)-induced oxidative damage than was observed for vitamin C, E, and β-carotene, or more than the individual compound, mangiferin **197** [191]. Like many studies regarding pharmacological effects of plant extracts, the reported activity is linked to the radical oxidative scavenging potency of the extract. Thus, it is logical to assess the protective effect of extracts or compounds against oxidative stress, as this is related to many diseases. Vimang® has

been tested for its mitochondrial oxidative stress prevention in atherosclerotic and/or hypercholesterolemic mice [192]. In red blood cells, both peel and bark extract have a protective effect against oxidation induced by hydrogen peroxide [193]. Oxidative stress is also a major factor in the development of neurodegenerative diseases such as Parkinson's syndrome. The anti-oxidative effect of mangiferin has been assessed against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity in N2A cells [194]. Mangiferin has not only shown anti-oxidative effects in neuron cells, but also inhibited cyclo-oxygenase-2 expression and prostaglandin E2 production in rat microglial cells [195]. This is not the only report of anti-inflammatory activity of mango tissues. Resorcinols isolated from mango peel have also been found to inhibit COX-1, COX-2 cyclo-oxygenases showing anti-inflammatory activity. Micromolar concentrations reduced prostaglandin E2 concentrations, for the first two, with IC_{50} values very close to the compounds used as positive controls (indomethacin and NS-398) [196]. In a larger series of experiments, the anti-allergic properties of both Vimang® and purified mangiferin **197** were assessed in vivo and in vitro. Effects were dose-dependent, but with concentrations up to 100-fold higher than the controls used [183]. In addition to the numerous reports of the cytoprotective effects of both extracts and individual compounds, there are also reports of anti-cancer properties via pro-apoptotic or genotoxic mechanisms. The genotoxicity of Vimang® has been evaluated in human lymphocytes. Very slight cytotoxic effects were seen, but no mutagenic or genotoxic effects were observed [174]. This is consistent with the suggestion [145] that polyphenols contained in food plants can have cancer-preventive action through an anti-mutagenic effect. Anti-cancer effects of mangiferin **197** have been determined in vivo using models of rat colon carcinogenesis [197]. A possible mechanism of action could be through pro-apoptotic properties as demonstrated both in Swiss albino mice and the LNCaP prostate cancer cell line [198]. Pardo-Andreu and co-workers also suggested that mangiferin **197** anti-oxidative properties may switch to a thiol arylation function, which would lead to permeability of the rat liver mitochondria that mediates apoptosis [199]. More reports of anti-cancer effects are listed by Masibo et al. [70] related to individual compounds isolated from mango, effective against breast cancer, colon cancer and leukemia. Another study showed a synergistic effect of mango extracts with anti-cancer drugs [200].

Pharmacological effects related to the symptoms of diabetes have also been investigated. Mangiferin **197** has been shown by Muruganadan and co-workers to have some protective effect against oxidative damage on cardiac and renal tissues [201], and anti-hyperglycemia and anti-atherogenicity in streptozotocin-induced diabetes in rats [202]. These results are in contrast with previous data, where an aqueous decoction of mango leaves had a positive effect on blood glucose reduction in normoglycaemic mice, and glucose-induced hyperglycaemic mice, but not in streptozotocin-induced diabetic mice [203]. Diabetes is closely linked to peroxisome-proliferator-activated receptors (PPARs). Wilkinson et al. have shown that mango components, mangiferin **197**, quercetin **94** and norathyriol **160** inhibit the activation of different PPAR isoforms [204]. Other less detailed investigations have included protection against activation-induced cell death [205], CYP3A metabolism inhibition [206], CYP2C9 metabolism inhibition [155], the cardiovascular protective effect of quercetin [207] and anti-microbial activity [97].

3.9 *Garcinia mangostana*

Mangosteen is an evergreen tree of the *Garcinia* genus, *Clusiaceae* family. It is known as the 'queen of fruit' with the predominant species being *G. mangostana*. Mangosteen is believed to have originated from the Indonesian archipelago. The fruits grow up to 8 cm wide and comprise a deep purple exocarp containing segments of white flesh resembling that of citrus but with a peachy taste. Although many phytochemicals have been isolated and identified, indicating an importance in nutrition, mangosteen fruit is not as well characterized as that of mango or banana [117, 118].

In addition to studies of phytochemical content, some pharmacological studies have also been published. Some of these studies have been reviewed by Chaverri et al. [20] who documented the main biological and medicinal properties of mangosteen leaves; these include the ubiquitous anti-oxidant activity, but also anti-cancer, anti-inflammatory and anti-allergy, anti-bacterial, anti-fungal and anti-viral, as well as anti-malarial activities. Since xanthones (cf. Section 2.3.8) are the main components identified in mangosteen, it is possible that pharmacological effects of xanthones reported for other systems are also responsible for cardioprotection, anti-atherosclerosis, and nitric oxide (NO) synthase inhibition in mangosteen [208]. Five xanthones isolated from the bark have been found to be slightly cytotoxic against the HT-29 colon cancer cell line, with IC_{50} values in the micromolar range, this is in contrast to camptothecin, which was used as a reference and was a hundred times more potent [209]. Similar IC_{50} concentrations have been reported for mangosteen pericarp extract against the SKBR3 breast cancer cell line [210] assessing pro-apoptotic induction. Among the anti-leukemic activity of 17 fruits, the mangosteen aqueous extract resulted in the highest activity against a K562 myelogenous leukemia cell line, with a selectivity index of 78.4 compared with the HEL 299 normal human lung cell line [160]. Many anti-inflammatory studies related to mangosteen pericarp and hull have been reported. Pericarp xanthones had an inhibitory effect on the signaling pathway of inflammatory mediators in RBL-2H3 cells. The degranulation of the cells that resulted was attributed to the suppression of an intracellular calcium elevation [211]. The hull was shown to have an effect on histamine release and prostaglandin E2 synthesis in the same cell line [212]. Tewtrakul et al. recently investigated further mediators of

the inflammatory pathway [85]. Two isolated compounds from mangosteen hull effectively inhibited the release of PGE2, TNFα, and IL-4, with inhibitory concentrations of a few ug/mL in RAW264.7 cells. The same compounds also inhibited mRNA expression of INOS and COX-2 [85]. LPS-mediated inflammation related to insulin resistance in primary cultures of human adipocytes was investigated. The results were interpreted as possibly inhibiting the activation of MAPK, NFKB and AP-1 [213]. Neuroprotective effects have also been reported for mangosteen. Pericarp extract possessed radical scavenging properties, which protected against 3-nitropropionic acid in cerebral granule neurons [214, 215]. Further investigation led to the identification of the xanthone α-mangostin as one of the active principles in the extract [214]. Among the very few clinical trials carried out to assess the nutritional benefit of tropical fruits on human health, Mangosteen Plus™, a commercial mangosteen juice, has been studied. The results showed a measurable improvement in immunological level of subjects who received the juice. Measuring multiple parameters such as T-cell subsets (γδ-T cells, DP T cells, Th cells, Tc cells, Th/Tc ratio), cytokine levels (IL-1α, IL-1β and IL-2), IgS complement (IgA, IgB, IgM, C3 and C4) and C-reactive protein (CRP) serum level authors report that the placebo group had a slight improvement as well, but less than the mangosteen juice group [216]. In addition to this improvement of the human immune system, mangosteen extracts and some xanthones were assessed for their interaction with cytochrome P450. The conclusion of this study was that mangosteen consumption should be considered with caution as an adjunct if taken in conjunction with traditional therapeutics since the xanthones showed an inhibitory effect on a number different CYP450 [217]. Very few in vivo studies exist regarding mangosteen, although cholesterol-fed rats were assessed for their plasma lipid composition after consumption of mangosteen (and snake fruit or Salak). The authors showed a clear benefit from consumption of both fruits, but human studies are needed to confirm those positive animal results [218]. On another level, mangosteen fruit have been investigated for anti-bacterial properties [219], with some specific xanthones showing activity at a few μg/mL and anti-parasitic properties against *P. falciparum*, *Trypanosoma brucei* and *T. cruzi*, and *Leishmania infantum* [220]. Finally, there are a few reports of specific protein inhibition effects, such as effects on α-amylase [221] (relevant to diabetes), or aromatase [87] (chemopreventive in postmenopausal women), but further studies need to be conducted to confirm the pharmacology behind these effects.

3.10 *Carica papaya*

Papaya is a large tree-like herb from the *Carica* genus, *Caricaceae* family. Papaya is native to the tropical Americas, and bear large pear-shaped amber skin fruit that contain numerous black peppery seeds. Flesh color of ripe fruit varies from orange to salmon pink or red. Papaya (or pawpaw) is well known in folk medicine for its numerous uses [117, 118].

Although papaya is a major tropical fruit around the world, only a few pharmacological studies have been undertaken in comparison to other tropical fruits. The main activity known for papaya is the use of latex for its wound healing properties [222]. In vivo studies in a mouse burn model suggest that the wound healing properties could possibly be related to collagen synthesis, through hydroxyproline content increase. The anti-mutagenesis effects listed for mango, also apply to papaya [145]. Ethyl acetate and heptane extracts of papaya both exhibited strong anti-mutagenic effects. Although not being the strongest inhibitor of CYP2C9 drug metabolism, the addition of papaya juice to human liver microsomes reduced the level of CYP2C9 diclofenac residual metabolism activity to less than 20%, and the residual activity of tolbutamide metabolism to less than 40% [155]. Some hematological differences in rats have been observed after a diet containing seed extract, or leaf extract or pulp extract [223]. Finally, papaya leaf ethanolic extract exhibited an anti-Leishmanial activity with an IC_{50} of 11 μg/mL, when compared with 94 other extracts [10]. Similar leaf extract from the Maradol cultivar also showed modest anti-fungal properties against *Fusarium* spp. with an MIC(50) of 625 μg/mL [224].

3.11 *Passiflora* genus

Passionfruit is a vine on which grows the passion flower, bearing the passionfruit. Belonging to the *Passiflora* genus, and *Passifloraceae* family, it is native to Brazil and north-eastern Argentina, although it is now cultivated in many tropical and subtropical regions of the world. Few types of passion fruit exist: the two main ones a yellow rind type that can grow up to the size of a grapefruit (*Passiflora flavicarpa*), and a purple rind type that is smaller than a lemon (*P. edulis*). Both types are nearly round, and within the rind cavity there are membranous sacs filled with a translucent orange-colored pulpy juice containing up to more than 200 small hard, dark pitted seeds that are eaten along with the juice [117, 118].

Passionfruit is well known for its anxiolytic and sedative effects. Accordingly, a number of studies report the use of *Passiflora* extracts in vivo. It is interesting, for example, to learn that *P. alata* leaf extract had a less pronounced effect than similar extracts from *P. edulis* leaves, but that it also had a biphasic effect on rats in the elevated plus maze test [112], used to evaluate the anti-anxiety properties of drugs in a rodent model. In a more recent, similar study, the authors also suggest that *Passiflora* species did not have the side effect of the control drug diazepam (memory loss) [225]. The pericarp of *P. edulis* has also been tested recently, showing the same anxiolytic and sedative properties, but without any

anti-convulsant properties [52]. The regular reports of *P. edulis* as a good anxiolytic are in contrast to an earlier comparative study of *P. incarnata* and *P. edulis* where the latter was found to be devoid of any significant bioactivity. This study also suggests that the biphasic effect of extracts could be due to a sedative rather than an anxiolytic effect [226]. Finally, Coleta et al. also report that the use of total flavonoid extract from *P. incarnata* has a stronger anxiolytic effect than subfractions, suggesting synergy of different compounds within the same extract [52, 54, 112, 225]. A detailed review was published in 2004 listing a whole range of ethnopharmacology, chemistry, toxicology and pharmacological reports [21]. Among other pharmacological effects, anti-inflammatory studies are noteworthy. In vivo experiments showed that *P. edulis* extracts affected the release and/or action of pro-inflammatory cytokines, enzymes and mediators of inflammation [53, 227, 228]. Anti-hypertensive effects have also been measured in rats, and attributed to the vasodilatory effect of polyphenols like luteolin **64**, and other compounds such as γ-aminobutyric acid [229]. The flour of the *Passiflora* pericarp was also tested in a clinical trial and was found to reduce total cholesterol and LDL-cholesterol levels [230]. However, it is unclear from the study which species was used, as an ambiguous definition of the plant was given (*P. edulis* or *P. flavicarpa*). Finally, it has been reported that a *P. edulis* leaf extract had a low activity as an anti-Leishmanial product ($IC_{50} = 150\,\mu g/mL$) when extracted with aqueous alcoholic solution [231], and against an acyclovir-resistant strain of HSV-1 with a selectivity index of 17.8 when extracted with aqueous solution [132].

3.12 *Diospyros kaki*

Persimmon is the fruit of a large number of species of trees of the *Diospyros* genus, Ebenaceae family. The most common species, kaki or Asian persimmon is a native of Asia, and, more specifically, China. Fruits are usually light yellow to dark orange, sometimes reddish, with a size ranging from a small plum to a large apple and are spherical or pumpkin-shaped [117, 118].

Persimmon has been studied previously and a review was published in 1998 listing the pharmacology and chemotaxonomy of the different plant species [61]. While the review provides a detailed list of ethnopharmacology, an interesting list of pharmacological studies is provided, ranging from anti-bacterial to anti-viral with an emphasis on anti-inflammatory or targeting the central nervous system, utilizing extracts from fruit, seed, bark, roots and leaves as well as isolated compounds [61]. Since then, persimmon has been further studied. For example, some anti-aging and anti-inflammatory effects ascribed to oligonol (which results from oligomerization of polyphenols especially proanthocyanidins) have been reported [232]. The leaf extract has also been reported to mediate histamine release in KU812 cell lines and to have some anti-dermatitis effect on rats [62]. The leaf extract polyphenols also showed some tyrosinase inhibitory effects that have been attributed to the glycone form of cyanidin. The aglycone cyanidin (**147**), as a pure compound, showed some strong tyrosinase inhibitory equivalent to the positive control quercetin (**94**), suggesting the potential use of persimmon leaves for pharmaceutical uses related to skin pigmentation [64]. The peel extracts and fractions have also shown some multidrug-resistant reversal effect on tumor cells through p-glycoprotein (Pgp)-dependent efflux, and some tumor-specific cytotoxicity [75]. The fruits from two different cultivars equally prevented hepatocyte steatosis and lowered plasma cholesterol levels [233]. The edible fraction of the fruit has also been measured for its anti-carcinogenesis effect on human lymphocytes, and its mechanism of action is suggested to be through the inhibition of DNA polymerase α and β [234]. The peel polyphenols show a cytoprotective effect against high glucose-induced oxidative stress, leading to a potential benefit of the fruit as a valuable source of anti-oxidants in diabetic individuals, related to the oxidative stress induced in hyperglycemia [235]. A persimmon peel extract has also been studied in a DNA microarray study to show that it can improve insulin resistance in vivo by increasing insulin receptor β-tyrosine phosphorylation and by upregulating the expression of insulin pathway related genes [236]. Finally, the wood extract isolated naphthalene compounds cited in Section 2.5, demonstrated moderate cytotoxic effects against colon cancer cell line HT-29 [114]. In both this article and the article from Xue et al. [64], it would have been very interesting to compare the crude extract to the individual compounds to assess the synergistic effect of the multiple polyphenols.

3.13 *Ananas comosus*

Pineapple plants, from the genus *Ananas*, *Bromeliaceae* family, are native to Paraguay and south Brazil. They bear cone-shaped fruits comprised many fruitlets resulting from individual flowers, are up to 30 cm height, with a tough waxy rind formed of hexagonal units that can be dark green, yellow, orange or even reddish when ripe. The fibrous flesh ranges from white to yellow [117, 118].

Despite its popularity, pineapple is not a tropical fruit plant that has been greatly screened for bioactivities. In one recent study, regarding the inhibition of tolbutamide and diclofenac hydroxylation cited above [155], pineapple was shown to be the most potent inhibitor of CYP2C9 cytochrome with only 5% v/v addition resulting in almost total inhibition of the CYP450 activity. The authors suggested that pineapple should be avoided as a juice or food when taking some prescribed drugs that are substrates for these enzymes to avoid drug interactions. This effect is unrelated to phytonutrients as the CYP450s retained complete activity when the juice was heated, but may be linked to the protease bromelain. Pineapple fruit extract did not have a strong

effect in an anti-mutagenesis study previously reported, with a very slight effect from the ethyl acetate fraction [145]. It is also surprising that pineapple showed no anti-proliferative effects in the HepG2 cell line [140].

4 Concluding remarks

Berries, apples and grapes are well-known examples of temperate fruits that have been extensively characterized both in terms of their phytochemical composition, and at a pharmacological or nutritional level. These fruits continue to be studied as they are promoted for their health benefits, principally related to their anti-oxidative properties, cardiovascular protection or anti-cancer properties. Their phytochemical composition mainly comprises polyphenols (flavonoids and subfamilies), stilbenoids, simple phenolic or hydroxycinnamic acids, isoprenoids (including carotenoids), alkaloids and more occasionally plant-specific, unique compounds like betalains from beetroot.

Polyphenols are not only present in temperate fruits and vegetables. A wide range of bioactive phytochemicals is ubiquitously found throughout the flowering plant kingdom. It is therefore not surprising to find the same classes of compounds in tropical fruits and vegetables. Not only similar classes of compounds are present, but chemical similarities are also found through individual derivatives of, e.g. quercetin **101**, genistein **150** and kaempferol **102**. Specific phytochemical classes are found in some tropical fruits. Some compounds were first identified in tropical fruits like the xanthones (cf. Section 2.3.8), which were first isolated and characterized from mangosteen pericarp. This suggests that tropical fruits represent an under-explored area of potential new phytochemicals. Compared with studies of temperate fruits and vegetables, reports on the chemical characterization of tropical fruits are less numerous. The detailed characterization of phytochemicals has increased in importance in the past fifteen to twenty years, mainly due to the rising interest that tropical fruits have received from consumers and consequently from the food industry.

Tropical fruits, as well as vegetables and herbs, have been used for centuries as traditional medicines (traditional Chinese medicine, Ayurveda). Across many civilizations, plants have been put to medicinal use, in some cases leading the way to today's therapeutic drugs. As reported in general reviews about tropical fruit plants, they are associated with numerous uses, depending on the plant parts and preparation, providing links to natural products and biological activities. Today, while temperate fruits have already been extensively characterized on a pharmacological level, with new studies being regularly published, modern pharmacognosy is not as well developed for tropical fruits. Studies have been conducted either in vitro or in vivo, and they mainly report pure compounds present in such fruits. Although reports of bioactivity from tropical fruit extracts exist and suggest a synergistic effect of such extracts, the nutritional aspects of such fruits are not frequently studied. Some tropical fruits, which are preponderant in international markets, such as bananas, have been more studied, while others, such as jaboticaba (*Myrciaria cauliflora*), have not been widely investigated to date.

The increase in demand from consumers for new flavours and textures from fruits and vegetables leads to a need to characterize such ''novel'' fruits in terms of their phytochemical constitution, nutritive values, bioactivity levels and food safety. Phytochemical composition analysis shows that tropical fruits are both similar and specific in their constitution as are temperate fruits. Nutritive values will provide important information regarding the status of these fruits. This could help develop a new ''super fruit'' category partly defined by higher content in nutrients and health benefits of certain fruits such as acai, mango, or pomegranate. Finally, the pharmacology of such fruits may lead to the discovery of new lead compounds with high specific activities and capable of further drug design and development. Although studies usually report a higher activity of extracts or fractions from fruits and vegetables, total extracts rather than pure compounds suggest a synergy of different, complementary activities. Thus, tropical fruit compounds could lead to unexplored synergies that should be harnessed.

Through the advanced methodologies employed for the extraction, isolation and identification of phytochemicals, the food industry is rapidly collecting data regarding such phytochemicals. These data are not only related to the most popular tropical fruits (mango, banana, passionfruit). Some less common fruits have also been studied at different levels either because of a specific chemistry (mangosteen) or because of their rapidly growing popularity and production (persimmon). In recent reports, fruits that have been less studied are mainly because their production or exportation is not of major importance (e.g. longan). One clear conclusion of ''data mining'' for the phytochemical composition of tropical fruits is that there is an immense variety of chemistries and that one single fruit is unlikely to be lacking in a diversity of phytochemicals. Thus, more detailed analyses of phytochemicals are warranted to increase our current knowledge. It is also clear that empirical techniques (Infrared IR, melting points with comparison to standards) used for the determination of phytochemical structures can no longer be considered as sufficient. HPLC retention time compared with standards is another step in identification, but definitive and clear identification should also include the use of NMR and mass spectrometry and, when possible, crystallography.

The use of emerging High Content Screening (HCS) technologies and high-throughput cellular signalling assays will be useful to answer our requirement for screening capabilities [237]. Indeed, through the use of such enabling technologies, multiple fractions, from multiple varieties, from multiple fruits can be assessed in a very short period of

time, providing that the model used is stable and representative of the activity tested. So far, HCS has been mainly used by pharmaceutical companies for screening lead compounds in drug design and development. But the use of such technologies from a nutritional point of view will be a powerful tool to help fill the gap of knowledge in the context of tropical fruit pharmacology and nutrition. However, all approaches used in screening fruit extracts for bioactivity need to have a clear appreciation that many phytochemicals will be metabolized either in the digestive tract (particularly by colonic microflora) or during or after absorption. This means that the molecules available for systemic bioactivity may differ markedly from the original constituents of fruits. Future studies may therefore need to take account of such post-digestion metabolism to further improve our understanding of how tropical fruits may benefit human health.

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