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# Genus *Melaleuca* - A Review on the Phytochemistry and Pharmacological Activities of the Non-Volatile Components

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**Abstract:** Plants of the genus *Melaleuca* which belong to family Myrtaceae, commonly named "tea trees", are economically important plants. When talking about tea trees, the essential oils are the center of attention, leaving all other phytoconstituents in their shade. Many reviews addressed the composition and pharmacological activities of *Melaleuca alternifolia* L. essential oil as the most common one. To date, there are no detailed reviews summarizing the phytochemical and pharmacological properties of the non-volatile components of members of the genus *Melaleuca*. After distillation of the volatile oil, large amounts of these plants' waste remain untapped. This review indicates that this genus is a rich source of diverse groups of bioactive phytochemicals, including flavonoids, triterpenoids, benzylic phloroglucinol-terpene derivatives, polyphenols, hydrolysable tannins, and other compounds. It also discusses the diverse pharmacological activities reported for plants of this genus.

**Keywords:** *Melaleuca*; Myrtaceae; tea tree; paperbark tree; phytochemistry; pharmacological activities. 

## 1. Introduction

Genus *Melaleuca,* as a member of family Myrtaceae, comprises 230 species. *Melaleuca alternifolia* L. is the most famous species and as other members of this genus, is native to Australia. In Australia, species in the genus *Melaleuca* are commonly named "tea trees" and "paperbark trees". The name "tea tree" originated when the sailors of Captain James Cook, during his journey to Australia in 1770, used this herb as a substitute for tea. Today, a variety of myrtaceous shrubs derived from the genera *Leptospermum*, *Melaleuca*, and *Kunzea* are collectively termed "tea trees", whereas the term "paperbark" arose from the bark that can be pulled off as papery strips [1]. One of these species is *M. leucadendron*, in which the bark peels off in papery layers [2]. The economic significance of plants which belong to *Melaleuca* spp. is due to their essential oils. The essential oil of *M. alternifolia* is the most common one. In addition, honey produced from the blossoms of the genus *Melaleuca* is of great value [1]. Research interest in the genus *Melaleuca* has been focused on the chemical composition and antimicrobial activity of the essential oils of these plants. Meanwhile, phytochemical investigation of

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the non-volatile content of the plants of this genus revealed the presence of mainly phenolics and terpenoidal compounds. The plant phenolics include flavonoids, phenylpropanoids, polyphenols, and free phenolic acids [1,3-6]. Melaleuca trees are also a rich source of triterpenoids, including lupane, ursane, and oleanane derivatives [7-11]. Another unique group namely benzylic phloroglucinol-terpene hybrids or meroterpenoids has been also reported from different plant parts of *M. leucadendron* [12,13]. Remarkably, the genus *Melaleuca* has shown several pharmacological activities, such as antimicrobial, antiparasitic, antioxidant, anti-inflammatory, acetylcholinesterase inhibition, neuroprotective, molluscicidal, antischistosomal, immunostimulant, anticancer, anti-histaminic, cardiovascular-, hepato-protective, antisecretory, and antiulcerogenic activities. Despite the various reviews that detailed the chemical composition and the pharmacological activities of the essential oils of the genus *Melaleuca*, no comprehensive review addressed the chemistry or the biological properties of the non-volatile components of this economically important genus. Therefore, this review summarized the different phytochemical groups and reported the pharmacological activities of this genus. Also, this review could direct the future research on genus *Melaleuca* towards the discovery of valuable medicinally active natural products especially from the plant waste left after distillation of the essential oil.

## 2. The Botany of Genus *Melaleuca*

Genus *Melaleuca* is classified according to Jones and Luchsinger (1986) as follows [14]:

- Kingdom: Plantae (Plants)
  - Division: Angiosperms (Magnoliophyta, flowering plants)
    - Class: Magnoliopsida (Dicotyledons)
      - Subclass: Rosidae
        - Order: Myrtales
          - Family: Myrtaceae (Myrtle family)
            - Subfamily: Leptospermoidae
              - Genus: *Melaleuca*

### *2.1. Order Myrtales*

They are woody and herbaceous plants. The leaves are mostly opposite and often glandular or dotted. The flowers are usually regular, tetra- or pentamerous, with valvate calyx. Stamens tend to be in groups or in bundles, sometimes dimorphous and open by terminal pores. The ovary is inferior, and the ovules are reduced in numbers in higher types. This order is spread over seven families, including Myrtaceae [2].

### *2.2. Family Myrtaceae (Myrtle Family)*

The family comprises about 140 genera and 3000 species. It is largely distributed in tropical and subtropical regions and abundant in Australia. They are shrubs to large trees. The leaves are usually opposite, sometimes alternate, simple, leathery, evergreen, entire, exstipulate, and characteristically glandular-dotted. Inflorescences are mostly cymose, sometimes racemose, and rarely solitary. Flowers are epigenous, sometimes perigynous, bisexual, and actinomorphic. The calyx is formed of 4-5 sepals, usually free, sometimes more or less united to form a cap which drops off as the flower opens. The corolla is formed of 4-5 petals. Stamens are indefinite. The ovary is formed of 2-3 united carpels, with one to many (often 2-5) locules, with 2-many ovules, the placentation is axile (rarely parietal), the ovary is commonly inferior, and the style is long and simple with a capitate stigma. Fruits are fleshy berries, rarely drupes, or dry capsules or nuts. Seeds have little or no endosperm. The family is classified into two subfamilies: Myrtoideae and Leptospermoideae [14].

*2.3. Subfamily Leptospermoidae*

The Leptospermoidae subfamily is characterized by spiral to opposite leaves, perigynous or epigynous flowers, and dry dehiscent fruits (capsules) [14,15]. This can be distinct from the Myrtoideae subfamily which has opposite leaves and indehiscent fruits [15].

*2.4. Genus Melaleuca*

Plants of the genus *Melaleuca* are shrubs or trees that possess spiral leaves. However, taxonomical studies should not be restricted to morphological characteristics, but molecular systematics based on their DNA comparison are very important in establishing the relationship between species [1].

## 3. Chemistry of the Family Myrtaceae

The Myrtaceae family contains various phytoconstituents, mainly phenolics and terpenoids [16,17]. Phenolics include flavonoids, phenylpropanoids, and polyphenols, such as phloroglucinol derivatives and free phenolic acids. Flavonoids are characterized by the presence of *O*- or *C*-methyl flavonoid, isoflavone, anthocyanin, and chalcone derivatives [18]. Additionally, polyhydroxy alkaloids (*e.g.* casuarine and fagomine) are of great chemotaxonomic importance to Myrtaceae [19]. The volatile oil of myrtaceous plants comprises various components, including monoterpenes, sesquiterpenes, and phenyl propanoids. Some genera produce very economically important volatile oil, such as clove oil, eucalyptus oil, tea tree oil, cajuput oil, niaouli oil, and pimento oil. Other constituents, such as bitter principles, free amino acids, hydrocarbons, and fatty acids, are also present [1,20].

## 4. Chemistry of the Non-volatile Components of gGenus *Melaleuca*

*4.1. Triterpenoids*

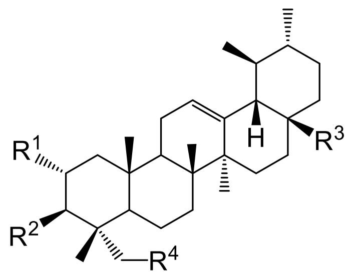
Triterpenoids are important $C_{30}$ naturally occurring isoprenoid plant metabolites with important chemistry and pharmacology [21, 22]. In particular, pentacyclic triterpenes have attracted many researchers in different areas of research, mainly as anticancer [7, 23], anti-inflammatory [24, 25], antiviral against HIV [26] and *Chlamydia trachomatis* [27]. The plants of the genus *Melaleuca*, reported with triterpenoidal contents, include *M. ericifolia* SM., *M. alternifolia* L., *M. leucadendron* L., *M. quinquenervia* Cav., *M. cajuputi* Powell., *M. cuticularis* Labill., *M. raphniphylla* Schauer. and *M. viminea* Lindl. [7-10, 28, 29] [4, 11, 30-32].

Triterpenoids from the genus *Melaleuca* possess different skeletons, including ursane (**1.1-1.12**, Table 1 and Figure 1), oleanane (**1.13-1.22**, Table 1 and Figure 2), and lupane (**1.23-1.34**, Table 1 and Figure 3). In addition, a group of miscellaneous triterpenoids has been also reported (**1.35-1.40**, Table 2 and Figure 4). Several triterpenoids from different plant parts, including leaves, heartwood, and fruits, exhibited the presence of esterifying $C_6$-$C_3$ acids at the hydroxyl group at C-3 namely *trans-p*-coumaric and *cis*/*trans*-caffeic acids. Another unique group of triterpenoids from this genus is 28-norlupane which is particularly identified from the leaves of *M. leucadendron* and *M. ericifolia* with a hydroxyl or peroxyl substituents at C-17, respectively. The presence of 27,28-dioic acids represented by melaleucic acid **1.29** ( 3$\beta$-hydroxylup-20(29)-en-27,28-dioic acid) and **1.19** (3$\alpha$-hydroxy-13(18)-oleanene-27,28-dioic acid), is also another characteristic chemical feature of the triterpenoids of the genus *Melaleuca*.

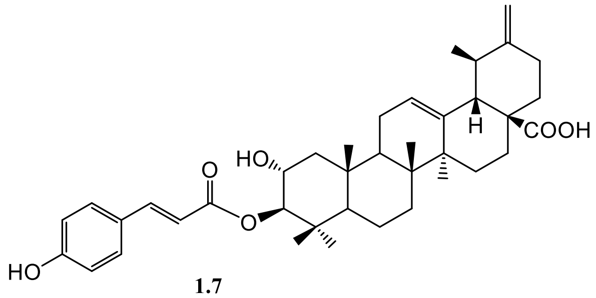
Although the triterpene nucleus was identified from many plants of the genus *Melaleuca*, there are no sufficient reports describing other non-volatile isoprenoid structures, such as diterpenes and oxygenated sequiterpenes. Meanwhile, acyclic isoprenoids of the corresponding biogenetic origin of sesquiterpne, diterpene and triterpenes have been detected in this genus, which include (2*E*,6*E*)-farnesol, **2.1** (C15) [11], phytol, **2.2** [11] (C20), and squalene, **2.3** [8, 11] (C30), respectively, Table 3 and Figure 5 .

**Table 1.** Pentacyclic triterpenoids from the genus *Melaleuca*.

| Compound | Name | Plant/ part | Ref. |
|---|---|---|---|
| **I- URSANE-TYPE PENTACYCLIC TRITERPENOIDS** | | | |
| **1.1** | Asiatic acid; 2$\alpha$,23-Dihydroxyursolic acid | Leaves of *M. ericifolia* | [7] |
| **1.2** | 3$\beta$-*O*-Acetylurs-12-en-28-oic acid | Bark and stem of *M. alternifolia* | [28] |
| **1.3** | 3$\beta$-*cis*-Caffeoyloxy-2$\alpha$-hydroxyurs-12-en-28-oate | Leaves of *M. leucadendron* | [10] |
| **1.4** | 3$\beta$-*trans*-Caffeoyloxy-2$\alpha$-hydroxyurs-12-en-28-oate | Leaves of *M. leucadendron* | [10] |
| **1.5** | 3-$\beta$-*cis*-*p*-Coumaroyloxy-2$\alpha$-hydroxyurs-12-en-28-oic acid | Leaves of *M. leucadendron* | [10] |
| **1.6** | 3-$\beta$-*trans*-*p*-Coumaroyloxy-2$\alpha$-hydroxyurs-12-en-28-oic acid | Leaves of *M. leucadendron* | [10] |
| **1.7** | 3-$\beta$-*cis*-*p*-Coumaroyloxy-2$\alpha$-hydroxyursa-12,20(30)-dien-28-oate | Leaves of *M. leucadendron* | [10] |
| **1.8** | 2$\alpha$,3$\beta$-Dihydroxyurs-12-en-28-oic acid | Heartwood of *M. leucadendron* | [8] |
| **1.9** | 2$\alpha$-Hydroxyursolic acid | Leaves of *M. leucadendron* | [10] |
| **1.10** | Ursolaldehyde | Leaves of *M. leucadendron* | [10] |
| | | Fruits of *M. leucadendron* | [9] |
| | | Leaves of *M. ericifolia* | [7] |
| **1.11** | Ursolic acid | Leaves of *M. leucadendron* | [10] |
| | | Fruits of *M. leucadendron* | [9] |
| | | Leaves of *M. quinquenervia* | [33] |
| | | Seeds of *M. cajuputi* | [29] |
| | | Leaves of *M. ericifolia* | [7] |
| **1.12** | Uvaol | Stems and leaves of *M. leucadendron* | [30] |
| **II- OLEANANE-TYPE PENTACYCLIC TRITERPENOIDS** | | | |
| **1.13** | 3$\beta$-*trans*-*p*-Coumaroyloxy-2$\alpha$,23-dihydroxyolean-12-en-28-oic acid | Heartwood of *M. leucadendron* | [8] |
| **1.14** | 23-*trans*-*p*-Coumaroyloxy-2$\alpha$,3$\beta$- dihydroxyolean-12-en-28-oic acid | Heartwood of *M. leucadendron* | [8] |
| **1.15** | 3$\beta$-*trans*-Caffeoyloxy-2$\alpha$,23-dihydroxyolean-12-en-28-oic acid | Heartwood of *M. leucadendron* | [8] |
| **1.16** | 3$\beta$-*cis*-Caffeoyloxy-2$\alpha$,23-dihydroxyolean-12-en-28-oic acid | Heartwood of *M. leucadendron* | [8] |
| **1.17** | 2$\alpha$,3$\beta$-Dihydroxyolean-12-en-28-oic acid | Heartwood of *M. leucadendron* | [8] |
| **1.18** | 3$\beta$,23-Dihydroxyolean-12-en-28-oic acid | Heartwood of *M. leucadendron* | [8] |
| **1.19** | 3$\alpha$–Hydroxy-13(18)-oleanene-27,28-dioic acid | Heartwood of *M. leucadendron* | [31] |
| **1.20** | Oleanolic acid | Leaf and stem of *M. quinquenervia* | [32] |
| **1.21** | 2$\alpha$,3$\beta$,23-Trihydroxyolean-12-en-28-oic acid | Heartwood of *M. leucadendron* | [8] |
| **1.22** | 2$\alpha$,3$\beta$,23-Trihydroxyolean-12-en-28-oic acid (arjunolic acid) | Bark and stem of *M. alternifolia* | [28] |
| **III- LUPANE-TYPE PENTACYCLIC TRITERPENOIDS** | | | |
| **1.23** | 3$\beta$-Acetyllup-20(29)-en-28-oic acid | Leaves of *M. leucadendron* | [11] |
| **1.24** | Betulin | Stems and leaves of *M. leucadendron* | [30] |
| | | Bark and stem of *M. alternifolia* | [28] |
| | | Leaves of *M. ericifolia* | [7] |
| **1.25** | Betulinaldehyde | Leaves of *M. leucadendron* | [11] |
| | | Fruits of *M. leucadendron* | [9] |
| | | Leaves of *M. ericifolia* | [7] |
| **1.26** | Betulinic acid | Leaves of *M. leucadendron* | [11] |
| | | Fruits of *M. leucadendron* | [9] |
| | | Bark and stem of *M. alternifolia* | [28] |
| | | Fruits of *M. leucadendron* | [4] |
| | | Seeds of *M. cajuputi* | [29] |
| | | Leaves of *M. ericifolia* | [7] |
| **1.27** | Betulonic acid; 3-Oxo-lup-20(29)-en-28-oic acid | Leaves of *M. leucadendron* | [11] |
| **1.28** | 20*S*-17$\beta$,29-Epoxy-28-norlupan-3$\beta$-ol | Leaves of *M. ericifolia* | [7] |
| **1.29** | Melaleucic acid; (3$\beta$-hydroxylup-20(29)-en-27,28-dioic acid) | Bark of (*M. cuticularis*, *M. raphniphylla* and *M. viminea*) | [34] |
| | | Bark and stem of *M. alternifolia* | [28] |
| | | Heartwood of *M. leucadendron* | [8] |
| | | Leaves of *M. ericifolia* | [35] |
| **1.30** | 28-Norlup-20(29)-ene-3$\beta$,17$\beta$-diol | Leaves of *M. leucadendron* | [11] |
| | | Leaves of *M. ericifolia* | [7] |
| **1.31** | 28-Norlup-20(29)-en-3$\beta$-hydroxy-17$\alpha$-hydroperoxide | Leaves of *M. ericifolia* | [7] |
| **1.32** | 28-Norlup-20(29)-en-3$\beta$-hydroxy-17$\beta$-hydroperoxide | Leaves of *M. ericifolia* | [7] |
| **1.33** | Platanic acid | Leaves of *M. leucadendron* | [11] |
| | | Leaves of *M. ericifolia* | [7] |
| **1.34** | Pyracrenic acid | Fruits of *M. leucadendron* | [9],[4] |

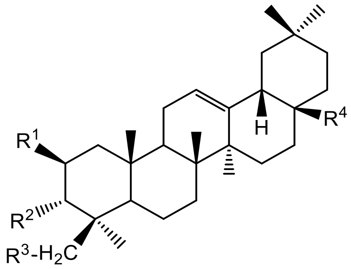



**1.1** $R^1$=OH, $R^2$=OH, $R^3$=COOH, $R^4$=OH
**1.2** $R^1$=H, $R^2$=$COOCH_3$, $R^3$=COOH, $R^4$=H
**1.3** $R^1$=OH, $R^2$= *cis*-caffeoyloxy, $R^3$=COOH, $R^4$=H
**1.4** $R^1$=OH, $R^2$= *trans*-caffeoyloxy, $R^3$=COOH, $R^4$=
**1.5** $R^1$=OH, $R^2$= *cis*-*p*-coumaroyloxy, $R^3$=COOH,
**1.6** $R^1$=OH, $R^2$= *trans*-*p*-coumaroyloxy, $R^3$=COOH
**1.8** $R^1$=OH, $R^2$=OH, $R^3$=COOH, $R^4$=H
**1.9** $R^1$=OH, $R^2$=OH, $R^3$=COOH, $R^4$=H
**1.10** $R^1$=H, $R^2$=OH, $R^3$=CHO, $R^4$=H
**1.11** $R^1$=H, $R^2$=OH, $R^3$=COOH, $R^4$=H
**1.12** $R^1$=H, $R^2$= OH, $R^3$=$CH_2OH$, $R^4$=H

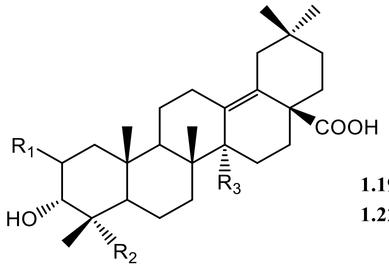



**1.7**

**Figure 1.** Structures of ursane-type pentacyclic triterpenoids (**1.1-1.12**) from the genus *Melaleuca*

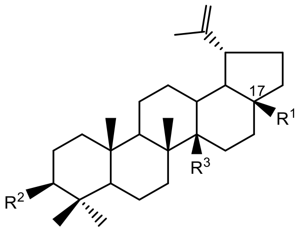



**1.13** $R^1$=OH, $R^2$=*trans*-*p*-coumaroyl, $R^3$=OH, $R^4$=COOH
**1.14** $R^1$=$R^2$=OH, $R^3$=*trans*-*p*-coumaroyl, $R^4$=COOH
**1.15** $R^1$=OH, $R^2$=*trans*-caffeoyl, $R^3$=OH, $R^4$=COOH
**1.16** $R^1$=OH, $R^2$=*cis*-caffeoyl, $R^3$=OH, $R^4$=COOH
**1.17** $R^1$=$R^2$=OH, $R^3$=H, $R^4$=COOH
**1.18** $R^1$=H, $R^2$=OH, $R^3$=OH, $R^4$=COOH
**1.20** $R^1$=H, $R^2$=OH, $R^3$=H, $R^4$=COOH
**1.21** $R^1$=OH, $R^2$=OH, $R^3$=OH, $R^4$=COOH

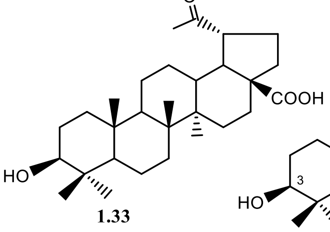



**1.19** $R^1$=H, $R^2$=$CH^3$, $R^3$=COOH
**1.22** $R^1$=OH, $R^2$=$CH_2OH$, $R^3$=$CH^3$

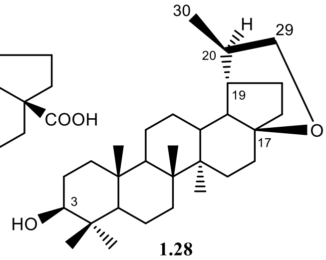
**Figure 2.** Structures of oleanane-type pentacyclic triterpenoids (**1.13-1.22**) from the genus *Melaleuca*




**1.23** $R^1$=COOH, $R^2$=OAc, $R^3$=$CH_3$
**1.24** $R^1$=$CH_2OH$, $R^2$=OH, $R^3$=$CH_3$
**1.25** $R^1$=CHO, $R^2$=OH, $R^3$=$CH_3$
**1.26** $R^1$=COOH, $R^2$=OH, $R^3$=$CH_3$
**1.27** $R^1$=COOH, $R^2$=O, $R^3$= =$CH_3$
**1.29** $R^1$= $R^3$=COOH, $R^2$=OH
**1.30** $R^1$=OH, $R^2$=OH, $R^3$=$CH_3$
**1.31** $R^1$= α–OOH, $R^2$=OH, $R^3$=$CH_3$
**1.32** $R^1$= β–OOH, $R^2$=OH, $R^3$=$CH_3$
**1.34** $R^1$=COOH, $R^2$= *O*-Caffeoyl, $R^3$=$CH_3$




**1.33**




**1.28**

**Figure 3.** Structures of lupane-type pentacyclic triterpenoids (**1.23-1.34**) from the genus *Melaleuca*

**Table 2.** Miscellaneous group of pentacyclic triterpenoids from the genus *Melaleuca*

| Compound | Name | Plant/ part | Ref. |
|---|---|---|---|
| **1.35** | 3$\alpha$,27-Dihydroxy-28,20$\beta$–taraxastanolide | Heartwood of *M. leucadendron*. | [31] |
| **1.36** | Eupha-7,24-diene-3$\beta$,22$\beta$-diol | Heartwood of *M. leucadendron*. | [31] |
| **1.37** | Friedelin | Stems and leaves of *M. leucadendron* | [30] |
| **1.38** | *Epi*-taraxeryl acetate | Stems of *M. leucadendron* | [30] |
| **1.39** | 20-Taraxastene-3$\alpha$,28-diol | Heartwood of *M. leucadendron* | [31] |
| **1.40** | Taraxastenone | Stems of *M. leucadendron* | [30] |

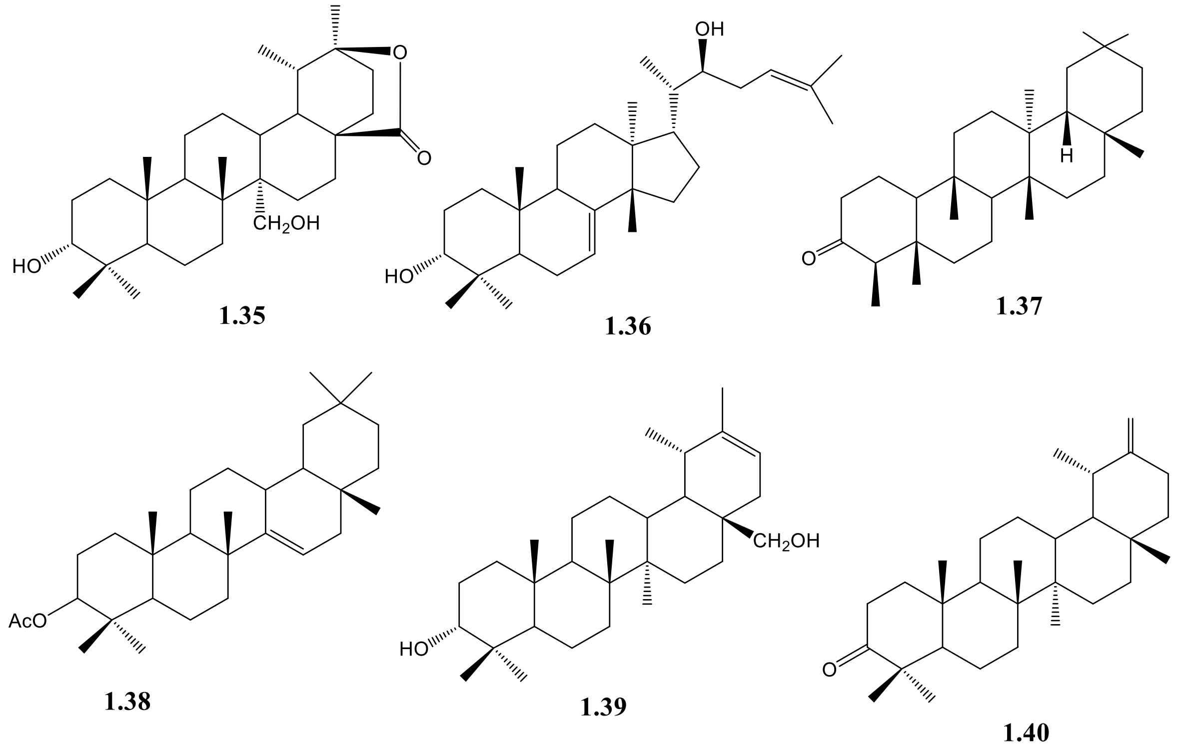



**Figure 4.** Structures of a miscellaneous group of pentacyclic triterpenoids (**1.35-1.40**) from the genus *Melaleuca*

*4.2. Acyclic terpenoids*

The reported acyclic terpenoids from the genus *Melaleuca* are few. Only three acyclic terpenoids have been reported, including squalene **2.3** ($C_{30}$), isolated from the heartwood and leaves of *M. leucadendron* [8, 11], phytol **2.2** ($C_{20}$) and (2*E*,6*E*)-farnesol **2.1** ($C_{15}$), isolated from the leaves of *M. leucadendron* Table 3 and Figure 5.

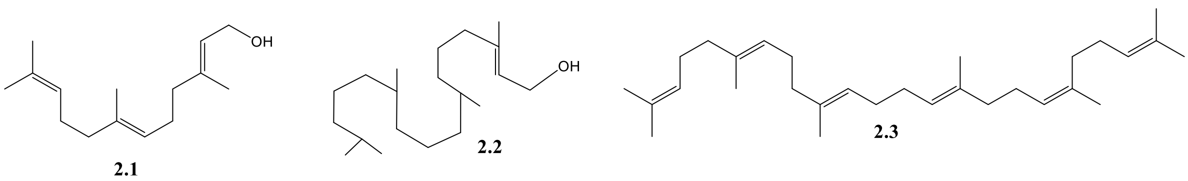



**Figure 5.** Structures of acyclic terpenoids (**2.1-2.3**) from the genus *Melaleuca*

### *4.3. Phytosterols*

Phytosterols are essential structural components in the plasma membrane of plant cells which are found free or conjugated through an ester or a glycosidic linkage. They are important precursors in the synthesis of many valuable bioactive compounds, such as steroidal alkaloids, steroidal saponins, plant-derived ecdysteroids, and brassinosteroids [36]. Four phytosterols have been identified form *Melaleuca* spp., including cholesterol $C_{27}$ (**3.1**), $\beta$-sitosterol $C_{29}$ (**3.2**), $\beta$-sitostenone $C_{29}$ (**3.3**), and stigmasterol $C_{29}$ (**3.4**), in Table 3 and Figure 6.

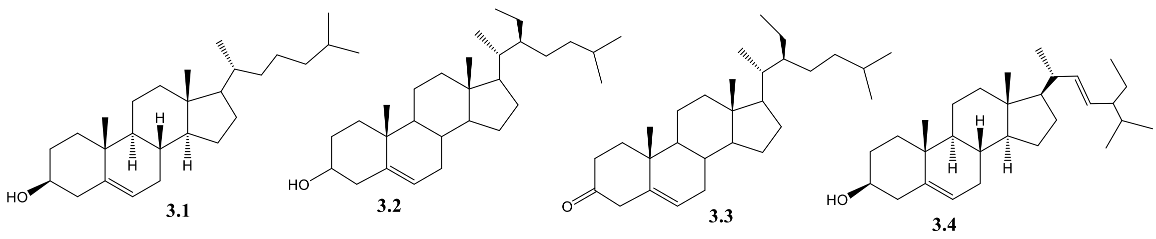



**Figure 6.** Structures of phytosterols (**3.1-3.4**) from the genus *Melaleuca*

**Table 3.** Acyclic terpenoids and phytosterols from the genus *Melaleuca*

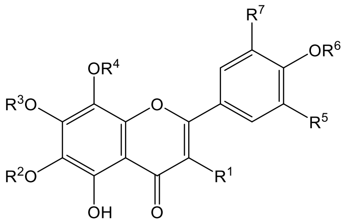
| Compound | Name | Plant/ part | Ref. |
|---|---|---|---|
| **ACYCLIC TERPENOIDS** | | | |
| **2.1** | (2*E*,6*E*)-Farnesol ($C_{15}$) | Leaves of *M. leucadendron* | [11] |
| **2.2** | Phytol ($C_{20}$) | Leaves of *M. leucadendron* | [11] |
| **2.3** | Squalene ($C_{30}$) | Heartwood of *M. leucadendron* | [8] |
| | | Leaves of *M. leucadendron* | [11] |
| **PYTOSTEROLS** | | | |
| **3.1** | Cholesterol | Leaf and stem of *M. quinquenervia* | [32] |
| **3.2** | $\beta$- Sitosterol | Stems and leaves of *M. leucadendron* | [30] |
| **3.3** | $\beta$- Sitostenone | Leaf and stem of *M. quinquenervia* | [32] |
| | | Heartwood of *M. leucadendron* | [8] |
| | | Leaves of *M. cajuputi* | [37] |
| | | Heartwood of *M. leucadendron* | [8] |
| **3.4** | Stigmasterol | Leaf and stem of *M. quinquenervia* | [32] |

### *4.4. Flavonoids*

Flavonoids are very essential and widely distributed plant $C_6$-$C_3$-$C_6$ metabolites. Due to their abundancy, flavonoids have been extensively investigated in literature. They possess diverse pharmacological actions, such as antioxidant, anticancer, enzyme inhibitory, neuroprotective, anti-atherosclerosis, anti-inflammatory, cardiovascular protective, and hepatoprotective effects [38-40]. Melaleuca is reported to contain different classes of flavonoids, including flavones, flavonols, and flavans (**4.1-4.47**), Table 4 and Figure 7. The predominant group is flavonols and the presence of methyl ethers was a characteristic feature of the reported flavonoids. Several flavonoid glycosides have been reported with several sugars, mainly as glucose, rhamnose, xylose, and glucuronic acid. However, it is worth noted that unlike other members of Myrtaceae, there are only few reports on *C*-methylated flavones and flavonols in tea trees represented by 5-hydroxy-7,4`-dimethoxy-6,8-dimethylflavone (**4.5**), isolated from the leaves of *M. cajuputi* [37]. Unlike flavones and flavonols, a class of methylated flavanones has been reported, Figure 8 and Table 4. This class was represented by strobopinin (**4.47**) and kryptostrobin (**4.41**), isolated from the flowers of *M. quinquenervia* [41]. Additionally, Seligmann and Wagner (1981) determined the structure of melanervin (**4.46**), the first naturally occurring flavonoid of the triphenylmethane family. Another class of unusual prenylated flavanones has been also reported from the leaves of *M. leucadenderon* represented by leucadenone A-D (**4.42-4.45**) [42], Table 4 and Figure 8.

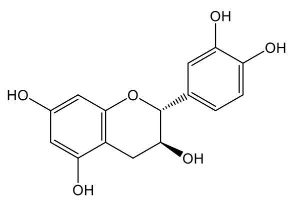
**Table 4.** Flavonoids from the genus *Melaleuca*

| Compound | Name | Plant/ part | Ref. |
|---|---|---|---|
| **I- FLAVONES** | | | |
| **4.1** | Apigenin | Leaves of *M. huegelii* | [3] |
| **4.2** | Apigenin-7-methyl ether | Leaves of *M. huegelii* | [3] |
| **4.3** | Apigenin-7,4`-dimethyl ether | Leaves of *M. huegelii* | [3] |
| **4.4** | Herbacetin-3-*O*-glucuronide | Leaves of *M. squarrosa* | [6] |
| **4.5** | 5-Hydroxy-7,4`-dimethoxy-6,8-dimethylflavone | Leaves of *M. cajuputi* | [37] |
| **4.6** | Kaempferol | Leaves of *M. huegelii* | [3] |
| | | Leaves of *M. leucadendron* | [43] |
| | | Leaf and stem of *M. quinquenervia* | [32] |
| | | Leaves of *M. ericifolia* | [35] |
| | | Leaves of *M. ericifolia* | [5] |
| **4.7** | Kaempferol-3-methyl ether | Leaves of *M. huegelii* | [3] |
| **4.8** | Kaempferol-3,7-dimethyl ether | Leaves of *M. huegelii* | [3] |
| **4.9** | Kaempferol-3,7,4`-trimethyl ether | Leaves of *M. huegelii* | [3] |
| **4.10** | Kaempferol-3-*O*-glucoside | Leaves of *M. leucadendra* | [44] |
| **4.11** | Kaempferol-3-*O*-xylosyl-(1```→2``)-glucoside | Leaves of *M. ericifolia* | [5] |
| **4.12** | Kaempferol -3-*O*-rhamnoside | Leaves of *M. ericifolia* | [5] |
| | | Leaves of *M. styphelioides* | [45] |
| **4.13** | Kaempferol-3-*O*-(2``-*O*-galloyl)-glucuronide | Leaves of *M. squarrosa* | [6] |
| **4.14** | Luteolin | Leaves of *M. huegelii* | [3] |
| | | Honey of *M. quinquenervia* | [46] |
| **4.15** | Luteolin-7,3`-dimethyl ether | Leaves of *M. huegelii* | [3] |
| **4.16** | Miquelianin | Leaves of *M. leucadendron* | [43] |
| **4.17** | Myricetin | Leaves of M. leucadendron | [43] |
| **4.18** | Myricetin 3-*O*-(2``-O-galloyl)-α-rhamnopyranoside | Leaves of *M. quinquenervia* | [47] |
| **4.19** | Myricitrin | Leaves of *M. leucadendron* | [43] |
| | | Leaves of *M. ericifolia* | [5] |
| | Myricetin 3-*O*-β-D-glucoside | Leaves of *M. quinquenervia* | [47] |
| **4.20** | | Leaves of *M. leucadendra* | [44] |
| **4.21** | Myricetin 3-*O*-β-D-glucuronide | Leaves of *M. quinquenervia* | [47] |
| **4.22** | Myricetin 3-*O*-rhamnoside | Leaves of *M. leucadendra* | [44] |
| **4.23** | Myricetin 3-rutinoside | Leaves of *M. leucadendra* | [44] |
| **4.24** | Myricetin-3-*O*-β-4C1-galactopyranuronoid | Leaves of *M. leucadendra* | [44] |
| **4.25** | Myricetin 3-*O*-xylosyl-(1```→2``)-glucoside | Leaves of *M. ericifolia* | [5] |
| | Quercetin | Leaves of *M. huegelii* | [3] |
| **4.26** | | Fruits of *M. leucadendron* | [9] |
| | | Leaves of *M. leucadendron* | [43] |
| | | Leaf and stem of *M. quinquenervia* | [32] |
| | | Leaves of *M. ericifolia* | [5] |
| | | Honey of *M. quinquenervia* | [46] |
| | | Leaves of *M. leucadendra* | [44] |
| **4.27** | Quercetin-3-methyl ether | Leaves of *M. huegelii* | [3] |
| **4.28** | Quercetin-3,7-dimethyl ether | Leaves of *M. huegelii* | [3] |
| **4.29** | Quercetin-3,7,3`-trimethyl ether | Leaves of *M. huegelii* | [3] |
| **4.30** | Quercetin-3,7,4`-trimethyl ether | Leaves of *M. huegelii* | [3] |
| **4.31** | Quercetin-3-*O*-xyloglucoside | Leaves of *M. leucadendron* | [43] |
| **4.32** | Quercitrin | Leaves of *M. leucadendron* | [43] |
| | | Leaf and stem of *M. quinquenervia* | [32] |
| | | Leaves of *M. quinquenervia* | [47] |
| | | Leaves of *M. ericifolia* | [5] |
| | | Leaves of *M. cajuputi* | [37] |
| | | Leaves of *M. leucadendra* | [44] |
| **4.33** | Quercetin-7-*O*-(6``-galloyl)-*β*-D-glucopyranoside | Leaves of *M. quinquenervia* | [47] |
| **4.34** | Quercetin-3-*O*-xylosyl-(1```→2``)-glucoside | Leaves of *M. ericifolia* | [5] |
| **4.35** | Quercetin-3-*O*-galactoside | Leaves of *M. ericifolia* | [5] |
| **4.36** | Quercetin-3-*O*-glucoside | Leaves of *M. ericifolia* | [5] |
| **4.37** | Quercetin-3-rutinoside, rutin | Leaves of *M. leucadendra* | [44] |
| | | Leaves of *M. leucadendra* | [44] |
| **4.38** | 5,7,3`,4`-Tetrahydroxyflavone 2`-*O*-β-D-glucuronide | Leaves of *M. quinquenervia* | [47] |
| **4.39** | Tricetin | Honey of *M. quinquenervia* | [46] |
| | | Honey of *M. quinquenervia* | [46] |
| | | Leaves of *M. ericifolia* | [5] |
| | | Leaves of *M. leucadendra* | [44] |
| **II-FLAVANS** | | | |
| **4.40** | Catechin | Leaves of *M. leucadendra* | [44] |
| **4.41** | Kryptostrobin | Flowers of *M. quinquenervia* | [41] |
| **4.42** | Leucadenone A | Leaves of *M. leucadenderon* | [42] |
| **4.43** | Leucadenone B | Leaves of *M. leucadenderon* | [42] |
| **4.44** | Leucadenone C | Leaves of *M. leucadenderon* | [42] |
| **4.45** | Leucadenone D | Leaves of *M. leucadenderon* | [42] |
| **4.46** | Melanervin | Flowers of *M. quinquenervia* | [41] |
| **4.47** | Strobopinin | Flowers of *M. quinquenervia* | [41] |

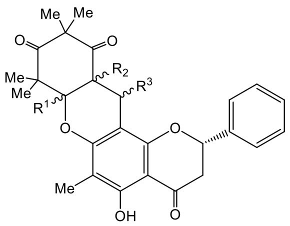



**4.1** $R^1=R^2=R^3=R^4=R^5=R^6=R^7=H$
**4.2** $R^1=R^2=R^4=R^5=R^6=R^7=H$, $R^3=CH_3$
**4.3** $R^1=R^2=R^4=R^5=R^7=H$, $R^3=R^6=CH_3$
**4.4** $R_1$= *O*-Glucur, $R^2=R^3=R^5=R^6=R^7=H$, $R^4=OH$
**4.5** $R^1=H$, $R^2=R^3=R^4=R^6=CH_3$, $R^5=R^7=H$
**4.6** $R^1=OH$, $R^2=R^3=R^4=R^5=R^6=R^7=H$
**4.7** $R^1=OCH_3$, $R^2=R^3=R^4=R^5=R^6=R^7=H$
**4.8** $R^1=OCH_3$, $R^3=CH_3$, $R^2=R^4=R^5=R^6=R^7=H$
**4.9** $R^1=OCH_3$, $R^3=R^6=CH_3$, $R^2=R^4=R^5=R^7=H$
**4.10** $R_1$= *O*-Glu, $R^2=R^3=R^4=R^5=R^6=R^7=H$
**4.11** $R_1$= *O*-Xyl-(1```→2``)-Glu, $R^2=R^3=R^4=R^5=R^6=R^7=H$
**4.12** $R_1$= *O*-Rha, $R^2=R^3=R^4=R^5=R^6=R^7=H$
**4.13** $R^1$= *O*-(2``-*O*-Galloyl)-Glucur, $R^2=R^3=R^4=R^5=R^6=R^7=H$
**4.14** $R^1=R^2=R^3=R^4=R^5=R^6=H$, $R^7=OH$
**4.15** $R^1=R^2=R^4=R^5=R^6=H$, $R^3=CH_3$, $R^7=OCH_3$
**4.16** $R^1$=*O*-*β*-D-Glucur, $R^7=OH$, $R^2=R^3=R^4=R^5=R^6=H$
**4.17** $R^1=R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.18** $R^1$=*O*-(2``-*O*-Galloyl)-Rha, $R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.19** $R^1$=*O*-Rha, $R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.20** $R^1$=*O*-Glu, $R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.21** $R^1$=*O*-Glucur, $R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.22** $R^1$=*O*-Rha, $R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.23** $R^1$=*O*-Glu-(1``→6`)-Rha, $R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.24** $R^1$=*O*-*β*-$^4C_1$-Galacutur, $R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.25** $R^1$=*O*-xyl-(1```→2``)-Glu, $R^5=R^7=OH$, $R^2=R^3=R^4=R^6=H$
**4.26** $R^1=R^7=OH$, $R^2=R^3=R^4=R^5=R^6=H$
**4.27** $R^1=OCH_3$, $R^2=R^3=R^4=R^5=R^6=H$, $R^7=OH$
**4.28** $R^1=OCH_3$, $R^3=CH_3$, $R^7=OH$, $R^2=R^4=R^5=R^6=H$
**4.29** $R^1=OCH_3$, $R^3=CH_3$, $R^7=OCH_3$, $R^2=R^4=R^5=R^6=H$
**4.30** $R^1=OCH_3$, $R^3=R^6=CH_3$, $R^7=OH$, $R^2=R^4=R^5=H$
**4.31** $R^1$=*O*-Xyl-Glu, $R^7=OH$, $R^2=R^3=R^4=R^5=R^6=H$
**4.32** $R^1$=*O*-Rha, $R^7=OH$, $R^2=R^3=R^4=R^5=R^6=H$
**4.33** $R^1=OH$, $R^3$=*O*-(6``-Galloyl)-Glu, $R^7=OH$, $R^2=R^4=R^5=R^6=H$
**4.34** $R^1$=*O*-Xyl-(1```→2``)-Glu, $R^7=OH$, $R^2=R^3=R^4=R^5=R^6=H$
**4.35** $R^1$= *O*-Gal, $R^7=OH$, $R^2=R^3=R^4=R^5=R^6=H$
**4.36** $R^1$= *O*-Glu, $R^7=OH$, $R^2=R^3=R^4=R^5=R^6=H$
**4.37** $R^1$= *O*-Glu-(1``→6`)-Rha, $R^7=OH$, $R^2=R^3=R^4=R^5=R^6=H$
**4.38** $R^1=R^2=R^3=R^4=R^6=H$, $R^5$=*O*-Glucur, $R^7=OH$
**4.39** $R^1=R^2=R^3=R^4=R^6=H$, $R^5=R^7=OH$

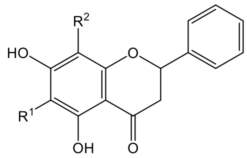
**Figure 7.** Chemical structures of flavones (**4.1-4.39**) from the genus *Melaleuca*



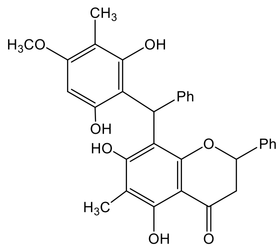

**4.40**




| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **4.42** | β-OH | α-H | α-Ph |
| **4.43** | α-OH | β-H | β-Ph |
| **4.44** | α-OH | α-H | α-Ph |
| **4.45** | α-OH | β-H | α-Ph |




**4.41** $R^1=H$, $R^2=CH_3$
**4.47** $R^1=CH_3$, $R^2=H$




**4.46**

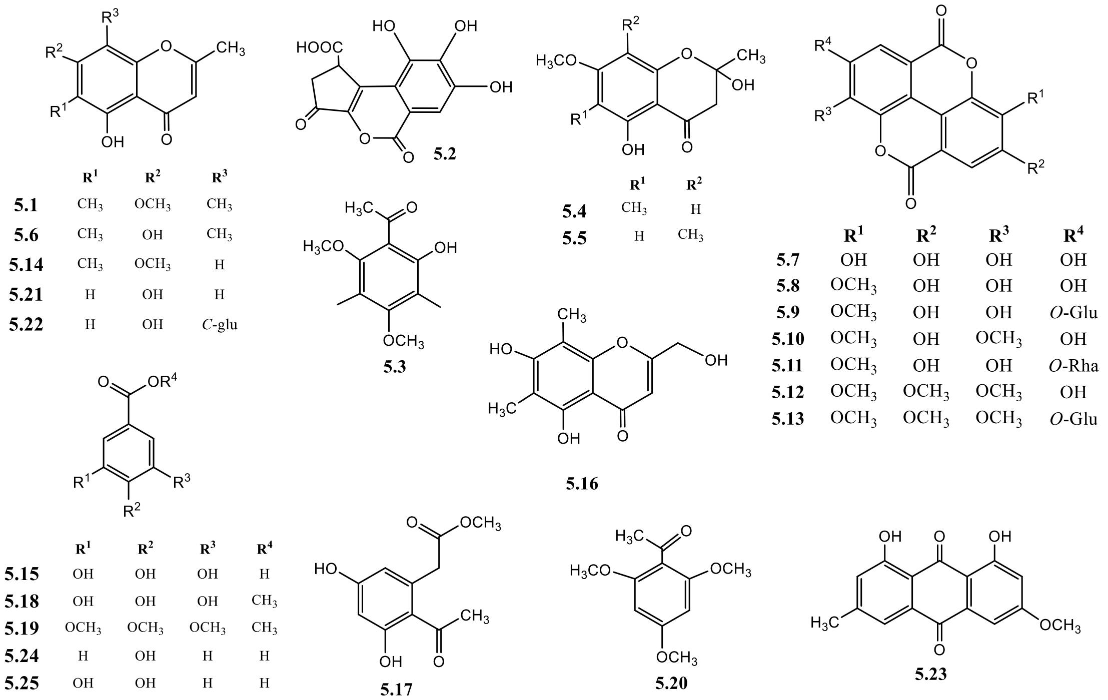
**Figure 8.** Chemical structures of flavans (**4.40-4.47**) from the genus *Melaleuca*

*4.5. Simple Phenolics and Phenylpropanoids*

Simple phenols are available in abundance in genus *Melaleuca* as represented by structures **5.1-5.37** (Table 5 and Figure 9 and 10). Phenylpropanoids are also present in this genus, which are simple secondary metabolites biosynthesized from shikimic acid pathway with the skeleton of $C_6$-$C_3$, such as the cinnamic acids, free (**5.26**, **5.27 and 5.33**) or conjugated as in case of chlorogenic acid (**5.28**). Additionally, various stilbenes and phenylpropanoids derivatives, including lignans and neolignans have been reported from this genus, Table 5 and Figure 10. A unique group of neolignans, known as melaleucins A-C (**5.35-5.37**), have been discovered from the leaves of *M. bracteata* F.Muell. [48]. Another reported group of simple phenols is 1,4-benzopyrone (γ-benzopyrone group), commonly known as chromones (**5.1, 5.4-5.6, 5.14, 5.16, 5.21** and **5.22**), have been identified from the leaves of *M. cajuputi* and *M. leucadendron.* Several members of family Myrtaceae have been reported to contain anthraquinones [49]. However, only one anthraquinone derivative (parietin, **5.23**) has been identified from the leaves of *M. cajuputi.* In addition, ellagic acid in its free, methylated, or glycosylated forms represent a major class of phenols found in this genus (**5.7-5.13**, Figure 9).

**Table 5.** Simple phenolics and phenylpropanoids from the genus *Melaleuca*.

| Compound | Name | Plant/ part | Ref. |
|---|---|---|---|
| **5.1** | Angustiforionol, 5-hydroxy-7-methoxy-2,6,8-trimethylchromone | Leaves of *M. cajuputi* | [37] |
| | | Leaf of *M. leucaderdron* | [50] |
| **5.2** | Brevifolincarboxylic acid | Fruits of *M. leucadendron* | [4] |
| **5.3** | Dimethylxanthoxylin | Leaf of *M. leucaderdron* | [50] |
| **5.4** | 2,5-Dihydroxy-7-methoxy-2,6-dimethylchromanone | Leaves of *M. cajuputi* | [37] |
| **5.5** | 2,5-Dihydroxy-7-methoxy-2,8-dimethylchromanone | Leaves of *M. cajuputi* | [37] |
| **5.6** | 5,7-Dihydroxy-2,6,8-trimethylchromone | Leaves of *M. cajuputi* | [37] |
| | | Honey of *M. quiquenervia* | [51] |
| **5.7** | | Leaves of *M. quinquenervia* | [52] |
| | Ellagic acid | Fruits of *M. leucadendron* | [4] |
| | | Honey of *M. quiquenervia* | [51] |
| **5.8** | Ellagic acid 3-*O*-methylether | Leaves of *M. quinquenervia* | [52] |
| **5.9** | Ellagic acid 3-monomethylether-4-*O*-glucoside | Leaves of *M. leucadendra* | [44] |
| **5.10** | Ellagic acid 3,3`-*O*-dimethylether | Bark and Stem of *M. alternifolia* | [28] |
| **5.11** | Ellagic acid 3-methoxy 4-*O*-$\alpha$-rhamnopyranoside | Leaves of *M. ericifolia* | [5] |
| | | | [35] |
| **5.12** | Ellagic acid 3,4,3`-tri-*O*-methylether | Leaves of *M. quinquenervia* | [52] |
| | | Leaves of *M. cajuputi* | [37] |
| **5.13** | Ellagic acid 3,3`,4`-trimethoxy- 4-*O*-$\beta$-glucoside | Leaves of *M. ericifolia* | [35] |
| **5.14** | Eugenitin | Leaves of *M. cajuputi* | [37] |
| | | Leaf of *M. leucaderdron* | [50] |
| **5.15** | Gallic acid | Leaves of *M. quinquenervia* | [52] |
| | | Fruits of *M. leucadendron* | [9] |
| | | Honey of *M. quiquenervia* | [51] |
| | | Leaves of *M. ericifolia* | [35] |
| | | leaves of *M. styphelioides* | [5] |
| | | Leaves of *M. ericifolia* | [45] |
| | | Leaves of *M. leucadendra* | [44] |
| **5.16** | Melachromone | Leaves of *M. cajuputi* | [37] |
| **5.17** | Methyl 2-acetyl-3,5-dihydroxyphenylacetate | Leaves of *M. cajuputi* | [37] |
| **5.18** | Methyl gallate | Leaves of *M. leucadendra* | [44] |
| **5.19** | Methyl tri-*O*-methyl gallate | Leaves of *M. ericifolia* | [35] |
| **5.20** | Methylxanthoxylin | Leaf of *M. leucaderdron* | [50] |
| **5.21** | Noreugenin | Leaves of *M. cajuputi* | [37] |
| **5.22** | Noreungenin 8-*C*-glucosyl | Leaf of *M. leucaderdra* | [44] |
| **5.23** | Parietin | Leaves of *M. cajuputi* | [37] |
| **5.24** | *p*-Hydroxybenzoic acid | Leaves of *M. ericifolia* | [5] |
| **5.25** | Protocatechuic acid | Fruits of *M. leucadendron* | [4] |
| **PHENYLPROPANOIDS and STILBENES** | | | |
| **5.26** | 3`,4`-Dimethoxy cinnamaldehyde | Leaves of *M. ericifolia* | [35] |
| **5.27** | Caffeic acid | Leaves of *M. leucadendra* | [44] |
| **5.28** | Chlorogenic acid | Honey of *M. quiquenervia* | [51] |
| **5.29** | Melaleucin A | Leaves of *M. bracteata* | [48] |
| **5.30** | Melaleucin B | Leaves of *M. bracteata* | [48] |
| **5.31** | Melaleucin C | Leaves of *M. bracteata* | [48] |
| **5.32** | Oxyresveratrol | Fruits of *M. leucadendron* | [9] |
| **5.33** | *p*-Coumaric acid | Honey of *M. quiquenervia* | [51] |
| **5.34** | Piceatannol | Fruits of *M. leucadendron* | [9],[4] |
| **5.35** | Piceatannol-4`-*O*-$\beta$-D-gucopyranoside | Fruits of *M. leucadendron* | [4] |
| **5.36** | Piceatannol-4'-*O*-$\beta$-D-gucopyranose-6``-*O*-gallate | Fruits of *M. leucadendron* | [4] |
| **5.37** | Scirpusin B | Fruits of *M. leucadendron* | [9] |



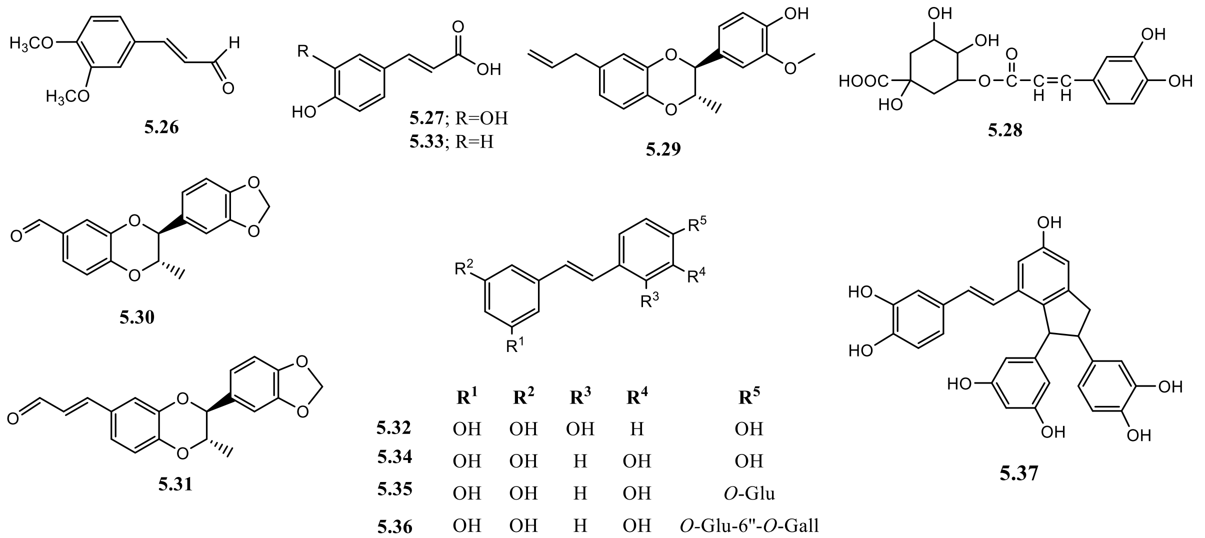

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **5.1** | $CH_3$ | $OCH_3$ | $CH_3$ |
| **5.6** | $CH_3$ | OH | $CH_3$ |
| **5.14** | $CH_3$ | $OCH_3$ | H |
| **5.21** | H | OH | H |
| **5.22** | H | OH | *C*-glu |

| | $R^1$ | $R^2$ |
|---|---|---|
| **5.4** | $CH_3$ | H |
| **5.5** | H | $CH_3$ |

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **5.7** | OH | OH | OH | OH |
| **5.8** | $OCH_3$ | OH | OH | OH |
| **5.9** | $OCH_3$ | OH | OH | *O*-Glu |
| **5.10** | $OCH_3$ | OH | $OCH_3$ | OH |
| **5.11** | $OCH_3$ | OH | OH | *O*-Rha |
| **5.12** | $OCH_3$ | $OCH_3$ | $OCH_3$ | OH |
| **5.13** | $OCH_3$ | $OCH_3$ | $OCH_3$ | *O*-Glu |

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **5.15** | OH | OH | OH | H |
| **5.18** | OH | OH | OH | $CH_3$ |
| **5.19** | $OCH_3$ | $OCH_3$ | $OCH_3$ | $CH_3$ |
| **5.24** | H | OH | H | H |
| **5.25** | OH | OH | H | H |

**Figure 9.** Structures of simple and polyphenolics (**5.1-5.25**) from the genus *Melaleuca*




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| **5.32** | OH | OH | OH | H | OH |
| **5.34** | OH | OH | H | OH | OH |
| **5.35** | OH | OH | H | OH | *O*-Glu |
| **5.36** | OH | OH | H | OH | *O*-Glu-6"-*O*-Gall |

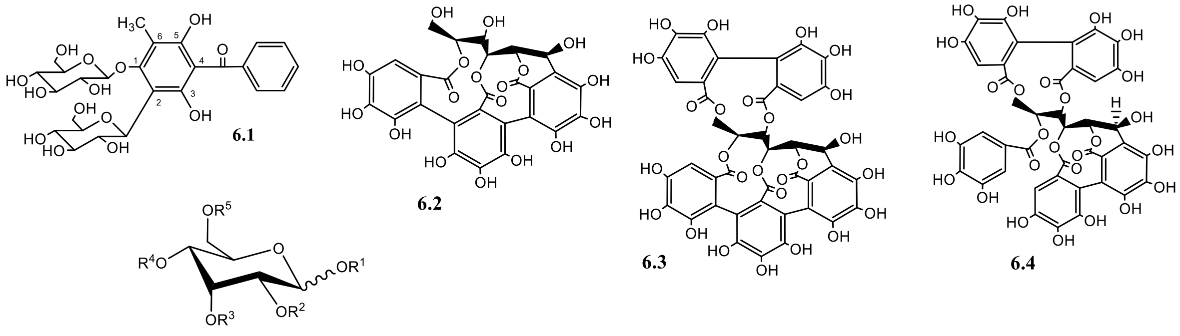
**Figure 10.** Structures of phenylpropanoids and stilbenes (**5.26-5.37**) from the genus *Melaleuca*.

*4.6. Hydrolysable Tannins*

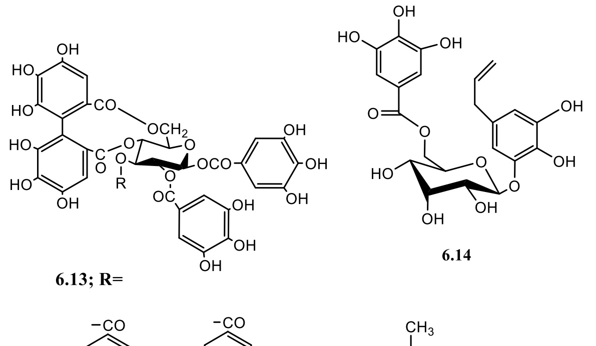
Hydrolysable tannins are known for their antioxidants effects and are widely distributed in the plant kingdom. Myrtaceae is considered as one of the common plant families known for its tannin contents, especially oligomeric ellagitannins [53]. In *Melaleuca* genus, hydrolysable tannins represent a major class of biomolecules with a fewer number of gallitannins (**6.5-6.12**) compared to ellagitannins (**6.1-6.4** and **6.13-6.30**), Table 6 and Figures 11-13. A great variation in the molecular weight of these compounds is observed. *Melaleuca squarrosa* Donn ex Sm. is characterized by the presence of *C*-glycosidic ellagitannins oligomers, such as melasquanins A and C (**6.18** and **6.19**) and squarrosanin A-C (**6.26-6.28**), respectively. Also, the leaves of *M. styphelioides* have been reported to contain several ellagitannins, such as pedunculagin (**6.21**), pterocarinin A (**6.23**), stachyurin (**6.25**), tellimagrandin I (**6.29**), and tellimagrandin II (**6.30**), in addition to the galloyl esters 1,2,3,6-tetra-*O*-galloyl-*β*-D-glucose (**6.11**), and 1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucose (**6.12**).

**Table 6.** Hydrolysable tannins from the genus *Melaleuca*

| Compound | Name | Plant/ part | Ref. |
|---|---|---|---|
| **6.1** | 4-Benzoyl-2-*C*-$\beta$-glucopyranosyl-3,5-dihydroxy-6-methylphenyl–*O*-$\beta$-D-glucopyranoside | Leaves of *M. quinquenervia* | [54] |
| **6.2** | Castalin | Leaves of *M. quinquenervia* | [52] |
| **6.3** | Castalagin | Fruits of *M. leucadendron* | [4] |
| **6.4** | Casuarinin | Fruits of *M. leucadendron* | [4]<br>[55]<br>[53] |
| **6.5** | 1,6-Di-*O*-galloyl-$\beta$-glucose | Leaves of *M. ericifolia* | [5] |
| **6.6** | 2,6-Di-*O*-galloyl-glucose | Leaves of *M. ericifolia* | [5] |
| **6.7** | 1-*O*-*p*-Hydroxybenzoyl-6-*O*-galloyl-$\beta$-glucose | Leaves of *M. ericifolia* | [5] |
| **6.8** | 2-*O*-*p*-Hydroxybenzoyl-6-*O*-galloyl-($\alpha/\beta$)-$^4C_1$-glucopyranose | Leaves of *M. ericifolia* | [5] |
| **6.9** | 2,3-Di-*O*-galloyl glucose | Leaves of *M. ericifolia* | [5] |
| **6.10** | 1,2,3-Tri-*O*-galloyl-$\beta$-D-glucose | Fruits of *M. leucadendron* | [4] |
| **6.11** | 1,2,3,6-Tetra-*O*-galloyl-$\beta$-D-glucose | Fruits of *M. Leucadendron*<br>Leaves of *M. styphelioides* | [4]<br>[45] |
| **6.12** | 1,2,3,4,6-penta-*O*-galloyl-$\beta$-D-glucose | Fruits of *M. Leucadendron*<br>Leaves of *M. styphelioides* | [4]<br>[45] |
| **6.13** | 1,2-Di-*O*-galloyl-3-*O*-digalloyl-4,6-*O*-hexahydroxydiphenoyl-$\beta$-D-glucose | Fruits of *M. leucadendron* | [4] |
| **6.14** | Ericifolin; eugenol-5-*O*-$\beta$-6`-*O*-galloylglucopyranoside | Leaves of *M. ericifolia* | [5] |
| **6.15** | Grandinin | Leaves of *M. quinquenervia*<br>Fruits of *M. leucadendron* | [52]<br>[4] |
| **6.16** | 2,3-*O*-Hexahydroxydiphenol-($\alpha/\beta$)-D-$^4C_1$-glucopyranose | Leaves of *M. quinquenervia* | [52] |
| **6.17** | 3-Hydroxy-5-methoxy-4-methylphenyl $\beta$-D-glucopyranoside | Leaves of *M. quinquenervia* | [54] |
| **6.18** | Melasquanin A | Leaves of *M. squarrosa* | [6]<br>[55] |
| **6.19** | Melasquanin C | Leaves of *M. squarrosa* | [6] |
| **6.20** | Oenothein | Fruits of *M. leucadendron* | [4] |
| **6.21** | Pedunculagin | Leaves of *M. styphelioides* | [45] |
| **6.22** | Praecoxin A | Leaves of *M. ericifolia* | [56] |
| **6.23** | Pterocarinin A | Leaves of *M. styphelioides* | [45] |
| **6.24** | Rugosin D | Fruits of *M. leucadendron* | [4] |
| **6.25** | Stachyurin | Leaves of *M. styphelioides*<br>Fruits of *M. leucadendron* | [4],[45]<br>[55],[53] |
| **6.26** | Squarrosanin A | Leaves of *M. squarrosa* | [6] |
| **6.27** | Squarrosanin B | Leaves of *M. squarrosa* | [6] |
| **6.28** | Squarrosanin C | Leaves of *M. squarrosa* | [6] |
| **6.29** | Tellimagrandin I | Leaves of *M. styphelioides* | [45] |
| **6.30** | Tellimagrandin II | Fruits of *M. Leucadendron*<br>Leaves of *styphelioides* | [4]<br>[45] |



| | R¹ | R² | R³ | R⁴ | R⁵ |
|---|---|---|---|---|---|
| **6.5** | Galloyl | H | H | H | Galloyl |
| **6.6** | H | Galloyl | H | H | Galloyl |
| **6.7** | *p*-(OH)-benzoyl | H | H | H | Galloyl |
| **6.8** | H | *p*-(OH)-benzoyl | H | H | Galloyl |
| **6.9** | H | Galloyl | Galloyl | H | H |
| **6.10** | Galloyl | Galloyl | Galloyl | H | H |
| **6.11** | Galloyl | Galloyl | Galloyl | H | Galloyl |
| **6.12** | Galloyl | Galloyl | Galloyl | Galloyl | Galloyl |



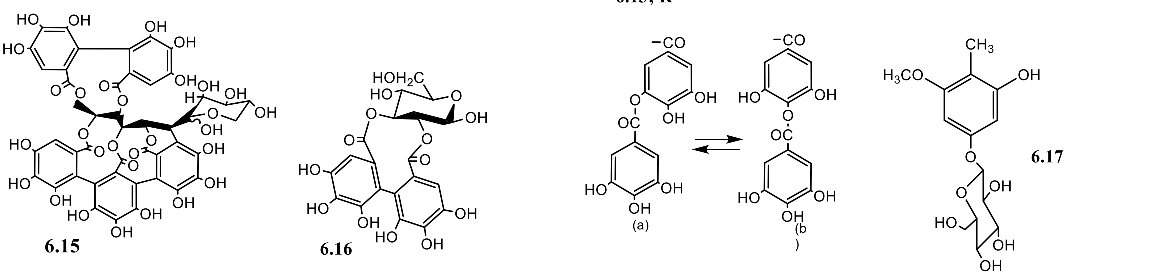


**Figure 11.** Structures of hydrolysable tannins (**6.1-6.17**) from the genus *Melaleuca*

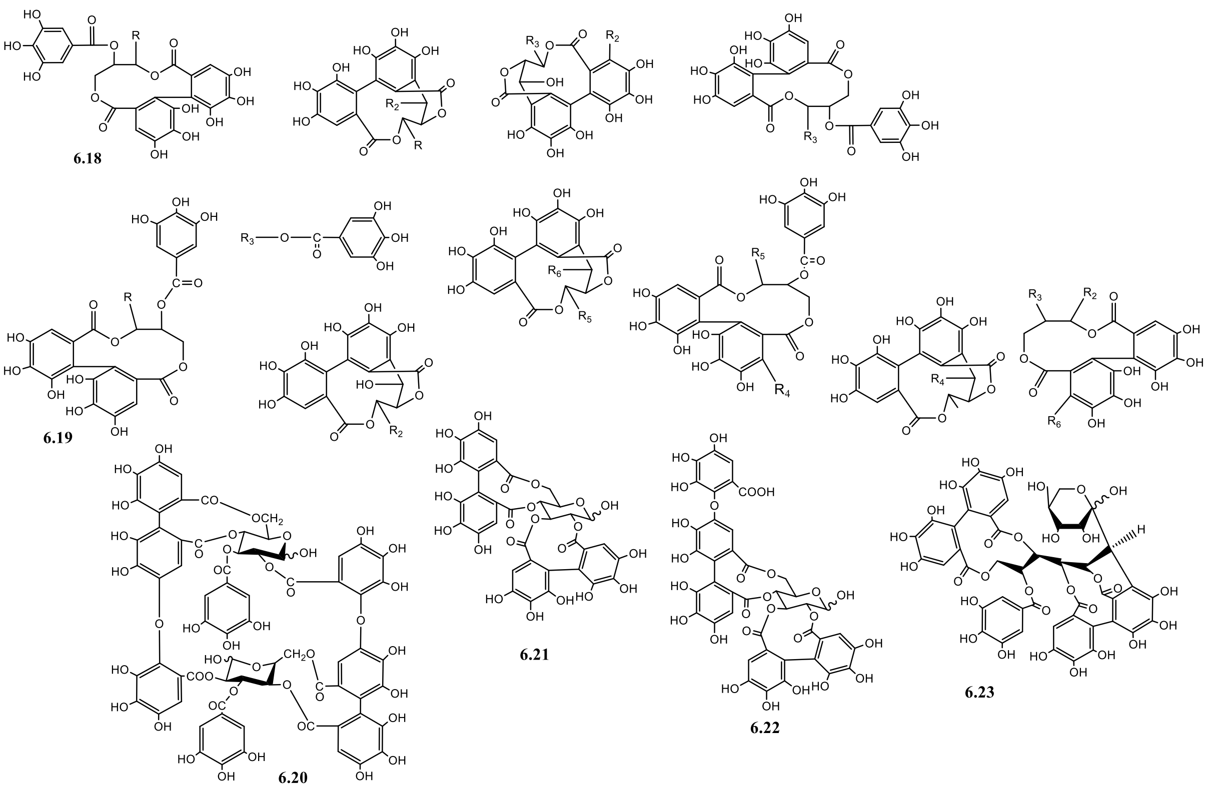


**Figure 12.** Structures of hydrolysable tannins (**6.18-6.23**) from the genus *Melaleuca*

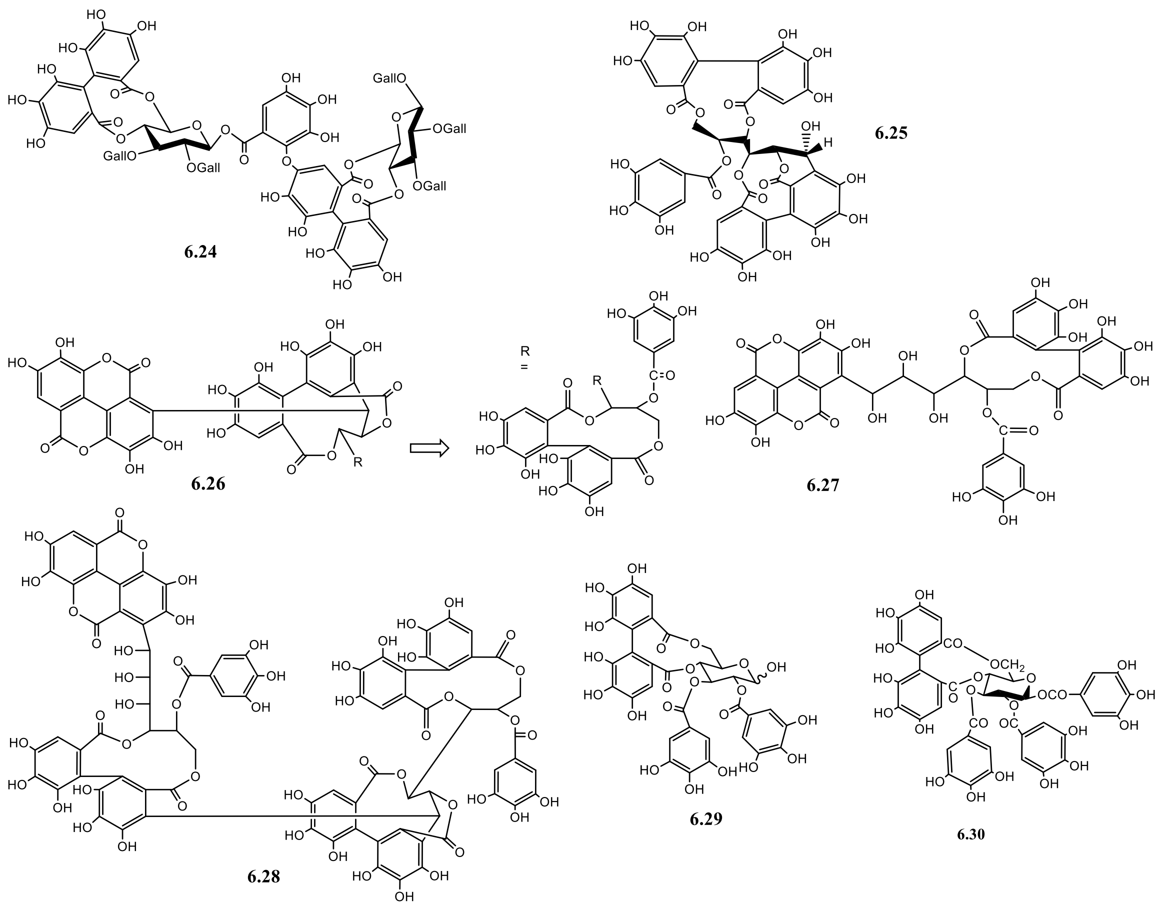



**Figure 13.** Structures of hydrolysable tannins (**6.24-6.30**) from the genus *Melaleuca*

### *4.7. Benzylic Phloroglucinol-Terpene Hybrids*

As a member of the family Myrtaceae, plants of the genus *Melaleuca* are rich in phloroglucinol derivatives, including phloroglucinol-terpene adducts [57]. A unique class of benzylic phloroglucinol-terpene hybrids namely leumelaleucols A-L (**7.1-7.13**) and melaleucadines A and B (**7.14** and **7.15)**, respectively, has been recently discovered [12,13], Table 7 and Figure 14. However, this class of meroterpenoids has been only identified from different parts of *M. leucadendron*, which paved the way towards more researches on other *Melaleuca* spp.

**Table 7.** Benzylic phloroglucinol-terpene hybrids from the genus *Melaleuca*

| Compound | Name | Plant/ part | Ref. |
|---|---|---|---|
| **7.1** | (+)-Leumelaleucol A | Fruits of *M. leucadendron* | [13] |
| **7.2** | (-)-Leumelaleucol A | Fruits of *M. leucadendron* | [13] |
| **7.3** | Leumelaleucols B | Fruits of *M. leucadendron* | [13] |
| **7.4** | Leumelaleucols C | Fruits of *M. leucadendron* | [13] |
| **7.5** | Leumelaleucols D | Fruits of *M. leucadendron* | [13] |
| **7.6** | Leumelaleucols E | Fruits of *M. leucadendron* | [13] |
| **7.7** | Leumelaleucols F | Fruits of *M. leucadendron* | [13] |
| **7.8** | Leumelaleucols G | Fruits of *M. leucadendron* | [13] |
| **7.9** | Leumelaleucols H | Fruits of *M. leucadendron* | [13] |
| **7.10** | Leumelaleucols I | Fruits of *M. leucadendron* | [13] |
| **7.11** | Leumelaleucols J | Fruits of *M. leucadendron* | [13] |
| **7.12** | Leumelaleucols K | Fruits of *M. leucadendron* | [13] |
| **7.13** | Leumelaleucols L | Fruits of *M. leucadendron* | [13] |
| **7.14** | Melaleucadine A | Branches and leaves of the *M. leucadendron* | [12] |
| **7.15** | Melaleucadine B | Branches and leaves of the *M. leucadendron* | [12] |

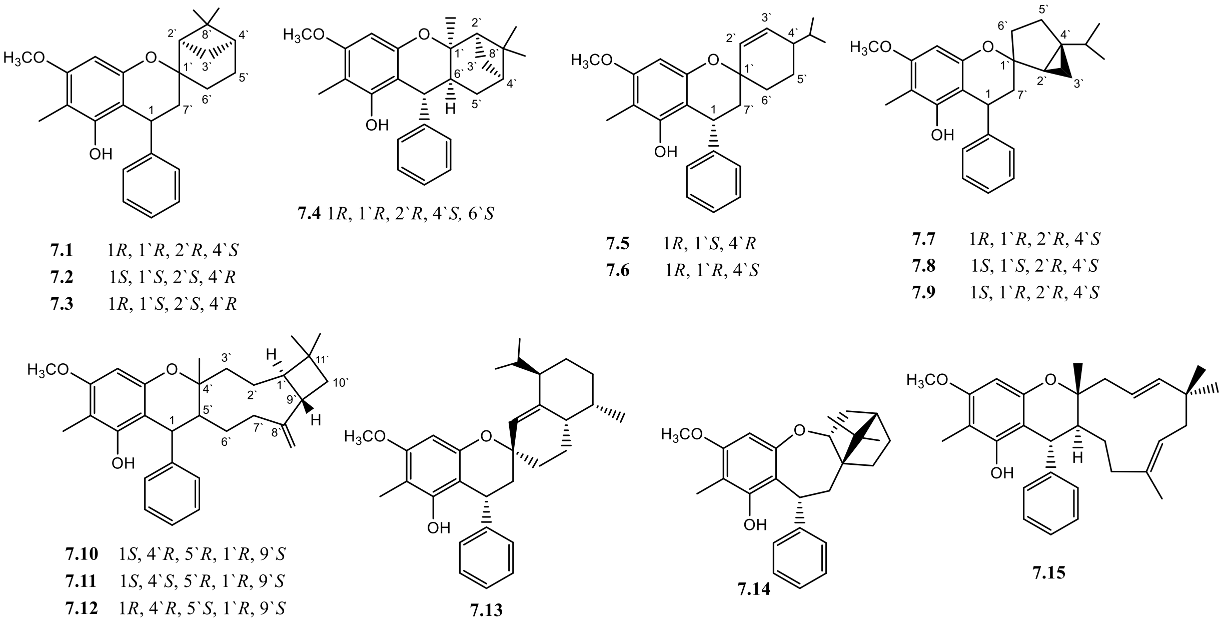



**Figure 14.** Structures of benzylic phloroglucinol-terpene hybrids (**7.1-7.15**)

### *4.8. Miscellaneous Group*

This class of miscellaneous compounds (Table 8 and Figure 15), comprising a group of simple terpenoidal glucosides, including citroside A (**8.1**), 2-endo-*β*-D-glucopyranosyloxy-1,8-cineole (**8.2**), 2-exo-*β*-D-glucopyranosyloxy-1,8-cineole (**8.3**), and roseoside (**8.4**), was identified from the leaves of *M. quinquenervia*. A minor group of alkaloids represented by proline derivatives (**8.5-8.8**) has been reported from several *Melaleuca* spp., including *M. alternifolia* L., *M. lanceolata* Otto., and *M. uncinata* R.Br.

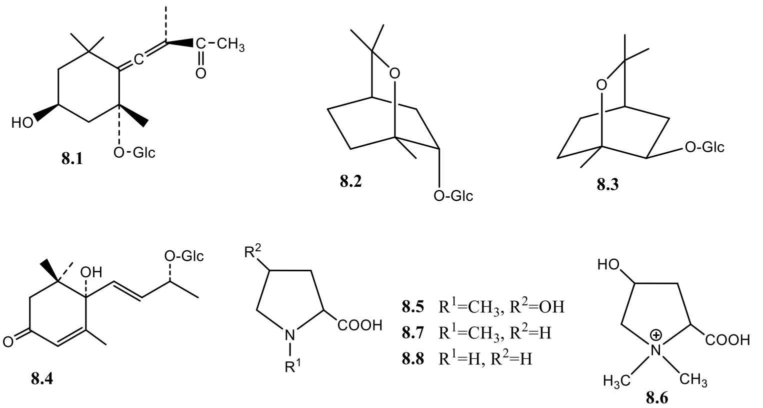



**Figure 15.** Structures of miscellaneous group (**8.1-8.8**) from the genus *Melaleuca*

A high content of fatty acids and hydrocarbon derivatives (**8.9-8.34**) was detected in several parts of these plants, Table 8 and Figure 16. The leaves and stems of *M. quinquenervia* showed the presence of palmitic acid as the major component of the saturated fatty acids content [32], whereas linolenic acid was the main constituent of the unsaturated fatty acids [32]. Gas chromatographic analysis of the hexane fraction of the barks and stems of *M. alternifolia* resulted in the identification of palmitate, stearate, and linolenate, in addition to several hydrocarbon derivatives, including 4-methyl-petan-3-one (**8.25**), undecan-2-one (**8.33**), hepta-2,4-dien-6-inal (**8.23**), and others [28]. Other miscellaneous compounds are represented by the aromatic hydrocarbon, naphthalene (**8.35**) [8].

**Table 8.** Miscellaneous group of compounds from the genus *Melaleuca*

| Compound | Name | Plant/ part | Ref. |
|---|---|---|---|
| I- **TERPENOIDAL GLUCOSIDES** | | | |
| **8.1** | Citroside A | Leaves of *M. quinquenervia* | [54] |
| **8.2** | 2-Endo-*β*-D-glucopyranosyloxy-1,8-cineole | Leaves of *M. quinquenervia* | [54] |
| **8.3** | 2-Exo-*β*-D-glucopyranosyloxy-1,8-cineole | Leaves of *M. quinquenervia* | [54] |
| **8.4** | Roseoside | Leaves of *M. quinquenervia* | [54] |
| II- **PROLINE DERVATIVES** | | | |
| **8.5** | 4-Hydroxy-*N*-methyl- proline | *Melaleuca* spp. | [58] |
| | | *M. lanceolata and M. uncinata* | [59] |
| | | *M. lanceolata* | [60] |
| **8.6** | 4-Hydroxy-*N*,*N*-dimethyl-proline (=Betonicine) | *Melaleuca* spp. | [58] |
| | | *M. lanceolata and M. uncinata* | [59] |
| | | Bark and stem of *M. alternifolia* | [28] |
| **8.7** | *N*-Methyl-L-proline | *Melaleuca* spp. | [58] |
| **8.8** | L-Proline | *Melaleuca* spp. | [58] |
| III- **FATTY ACIDS** | | | |
| **8.9** | Capric acid | Leaf and stem of *M. quinquenervia* | [32] |
| **8.10** | Lauric acid | Leaf and stem of *M. quinquenervia* | [32] |
| **8.11** | Linoleic acid | Leaf and stem of *M. quinquenervia* | [32] |
| **8.12** | Linolenic acid | Leaf and stem of *M. quinquenervia* | [32] |
| | | Bark and stem of *M. alternifolia* | [28] |
| **8.13** | Oleic acid | Leaf and stem of *M. quinquenervia* | [32] |
| **8.14** | Pelargonic acid | Leaf and stem of *M. quinquenervia* | [32] |
| **8.15** | Palmitic acid | Leaf and stem of *M. quinquenervia* | [32] |
| **8.16** | Palmitoleic acid | Leaf and stem of *M. quinquenervia* | [32] |
| | | Bark and stem of *M. alternifolia* | [28] |
| **8.17** | Stearic acid | Leaf and stem of *M. quinquenervia* | [32] |
| | | Bark and stem of *M. alternifolia* | [28] |
| IV- **HYDROCARBONS AND THEIR DERIVATIVES** | | | |
| **8.18** | Decane (C10) | Bark and stem of *M. alternifolia* | [28] |
| **8.19** | Docosane (C22) | Leaf and stem of *M. quinquenervia* | [32] |
| **8.20** | Dodecane | Bark and stem of *M. alternifolia* | [28] |
| **8.21** | Eicosane (C20) | Leaf and stem of *M. quinquenervia* | [32] |
| **8.22** | Hexadecane (C16) | Leaf and stem of *M. quinquenervia* | [32] |
| **8.23** | Hepta-2,4-dien-6-inal | Bark and stem of *M. alternifolia* | [28] |
| **8.24** | 6-Hydroxy-4,6-dimethyl-3-hepten-2-one | Heartwood of *M. leucadendron* | [8] |
| **8.25** | 4-Methyl-pentan-3-one | Bark and stem of *M. alternifolia* | [28] |
| **8.26** | 6-Methyldec-4-ene ($^4\Delta$ C11) | Bark and stem of *M. alternifolia* | [28] |
| **8.27** | Methyl 6-hydroxyhexanoate | Bark and stem of *M. alternifolia* | [28] |
| **8.28** | Octadecane (C18) | Leaf and stem of *M. quinquenervia* | [32] |
| **8.29** | Octcosane (C28) | Leaf and stem of *M. quinquenervia* | [32] |
| **8.30** | Tridecane (C13) | Bark and stem of *M. alternifolia* | [28] |
| **8.31** | Tetradecane (C14) | Leaf and stem of *M. quinquenervia* | [32] |
| | | Bark and stem of *M. alternifolia* | [28] |
| **8.32** | Triacontane (C30) | Leaf and stem of *M. quinquenervia* | [32] |
| **8.33** | Undecan-2-one | Bark and stem of *M. alternifolia* | [28] |
| **8.34** | Undecane (C11) | Bark and stem of *M. alternifolia* | [28] |
| V- **OTHER MISCELLANEOUS COMPOUNDS** | | | |
| **8.35** | Naphthalene | Heartwood of *M. leucadendron* | [8] |

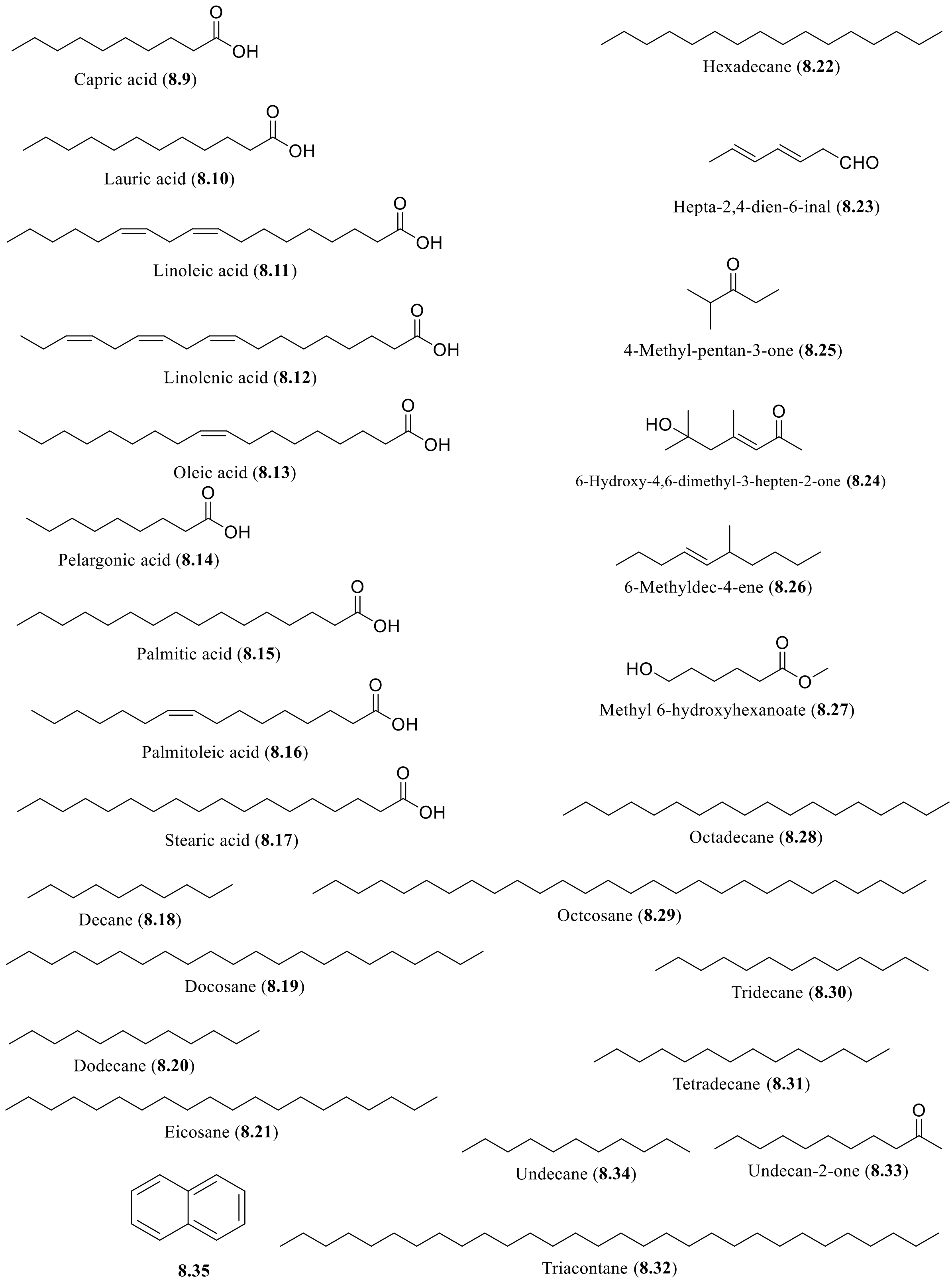



**Figure 16.** Structures of fatty acids and hydrocarbon derivatives (**8.9-8.35**)

It is worth mentioning that some compounds have been identified from the essential oils of *Melaleuca* spp., such as anthraquinones, coumarins, and alkaloids, which are commonly distilled with the oil. Additionally, other compounds, including diterpenes, fat, and other non-volatile compounds can be isolated from volatile oils using methods other than distillation [61].

## 5. Pharmacological Activities of the Non-volatile Components

Diverse biological activities have been reported for plants of the genus *Melaleuca*. The reported activities, including antimicrobial, antiparasitic, antioxidant, anti-inflammatory, acetylcholinesterase inhibition, neuroprotective, molluscicidal, antischistosomal, immunostimulant, anticancer, antihistaminic, cardiovascular, hepatoprotective, antisecretory, antiulcerogenic, and liver microsomal enzyme inhibition activity, are discussed herein in detail.

The reported biological assays were conducted either on the crude extracts from different plant parts, such as leaves, flowers, stems, and barks, or using pure isolated compounds of known pharmacological actions, such as betulinic acid, ursolic acid, oxyresveratrol, piceatannol, flavonoids, and ellagitannins. Betulinic acid is an attractive point for many researchers towards the derivatization and biological evaluation of several pharmacological activities, especially those related to anticancer drug discovery [7, 62].

### *5.1. Antimicrobial and Antiparasitic Activity*

The methanol extracts of the flowers and the leaves of *M. cajuputi* exhibited antibacterial effects against *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Bacillus cereus*. It was suggested that the antimicrobial activities may be attributable to the high flavonoid and phenolic contents of these extracts [63]. Also, the methanol extract of *M. cajuputi* flowers exhibited inhibitory activity against the filarial worm *Brugia pahangi* through reduction in worm motility and viability and in microfilarial release. Furthermore, *M. cajuputi* flower extract inhibited the endosymbiont *Wolbachia* bacteria of *B. pahangi* through significant reduction in worm viability, enhancing the antifilarial activity [64]. The methanol extract of the fresh *M. cajuputi* leaf waste, left after distillation of the essential oil, exhibited a low to strong antibacterial activity against the tested Gram positive bacteria, including *Bacillus sp.*, *Enterococcus faecalis*, *S. aureus*, and Gram negative bacteria, including *Vibrio cholerae* and *Shigella dysentriae* [65]. In addition, three isolated neolignans from the leaves of *M. bracteata* named melaleucins A–C (**5.35-5.37**) were investigated for their antibacterial activity against *S. aureus*, *E. coli*, and methicillin-resistant *S. aureus* (MRSA). Both melaleucins A and C exhibited significant inhibitory activities against *S. aureus* and MRSA [48]. Laribi et al. (2020) compared the antifungal activities of the volatile oil and non-volatile extracts of *M. styphelioides* Sm. leaves against *Aspergillus niger*, *Rhizopus nigricans*, and *Penicillium digitatum*. The tested samples showed different selectivity for each microorganism studied, where the volatile oil was predominantly effective against *A. niger*, whereas *P. digitatum* was found to be the most susceptible species for the aqueous extract and *R. nigricans* was more susceptible to the methanol extract [66].

### *5.2. Antioxidant and Anti-inflammatory Effects*

Grandinin (**6.20**), the major polyphenol in *M. quinquenervia* leaves, was found to display antioxidant activity [52]. Also, the *C*-glucosidic ellagitannins isolated from the leaves of *M. squarrosa*, including complex tannins and oligomers have been shown to be more effective radical scavengers in 2,2-diphenyl-*1*-picrylhydrazyl (DPPH) assay than its flavonoids and ordinary ellagitannins [6]. Al-Abd et al. (2015) investigated the antioxidant and radical scavenging activity of the methanol extracts of *M. cajuputi* using DPPH radical scavenging, β-carotene bleaching, and ferric reducing antioxidant power (FRAP) assays. The flower extract showed a better activity than that of the leaf extract explained by the higher total phenolic contents in the flower extract compared to that of the leaf extract [63]. The nephroprotective effect of phenolic compounds isolated from the leaf extract of *M. styphelioides*, including pedunculagin (**6.21**), pterocarinin A (**6.23**), tellimagrandin I (**6.29**), and casuarinin (**6.4**), towards diabetes mellitus and kidney stone oxidative stress-mediated kidney damage has been studied on a glucose- and oxalate-challenged NRK-49F cell model [67]. The results showed that the tested compounds restored catalase and superoxide dismutase antioxidant activity, reversed lipid peroxidation, and protected the kidney fibroblast cells from glucose- and oxalate-mediated stress [67]. Also, the methanolic extract of the leaves of *M. styphelioides* exhibited antioxidant activity using DPPH, $ABTS^{\cdot+}$, and FRAP assays. It inhibited pro-inflammatory mediators, including iNOS, NF-kB, COX-2, and inter-cellular adhesion molecule-1 (ICAM-1) in interferon gamma/histamine (IFN-g/H)-stimulated inflammation in NCTC 2544 human keratinocytes. LC/MS-MS analysis of the tested extract suggested that the phenolic compounds, mainly as quercetin, gallic acid, and ellagic acid, are responsible of these activities [68]. The ethanolic extract of *M. leucadendron* flowers exhibited an *in vitro* photoprotective effect towards UVB-induced oxidative stress in human skin keratinocytes (HaCaT). This has been concluded from the obtained DPPH antioxidant capacity, the maintained levels of ROS, GSH, glutathione peroxidase (GPx), SOD, catalase, and COX-2 expressions and reduced impairment of transmembrane transport and pro-apoptotic protein expression of the tested cells [69]. Casuarinin (**6.4**), an ellagitannin isolated from *M. leucadendra* L. leaves, suppressed the expression of NF-κB, COX-2, and iNOS to their normal levels. It also increased the level of reduced glutathione, catalase, and prostaglandin $E_2$ in ethanol-induced gastric ulcer in rats [70]. Herbal infusion of *M. citrolens* Barlow. leaves (gulbarn) infusions showed similar antioxidant activity as commercial green tea [71]. Similarly, the leaf extract of *M. leucadendra* and its isolate myricetin-3-*O*-β-$^4C_1$-galactopyranuronoid (**4.24**) exhibited strong antioxidant activity using DPPH and oxygen radical absorption capacity (ORAC) assay [44]. Regarding the non-phenolic components, betulinic acid (**1.26**) isolated from *M. bracteata* displayed antioxidant potential through preventing catalase inhibition as catalase enzyme catalyzes the decomposition of harmful $H_2O_2$ into $H_2O$, and $O_2$ [72]. Also, evaluation of the anti-inflammatory activity of betulinic acid isolated from *M. bracteata* using cotton pellet-induced granuloma model showed significant dose-dependent inhibition. Furthermore, betulinic acid significantly inhibited COX-1 and COX-2 activity in concentration-dependent manner [72]. Additionally, betulinic acid exhibited antioxidant activity through preventing SOD inhibition [72 73]. Superoxide dismutase (SOD) acts as an inhibitory agent of neutrophil-mediated inflammation and serves as an antioxidant through splitting superoxide radicals into the less harmful $O_2$ and $H_2O$ [72, 73].

### *5.3. Acetylcholinesterase and Neuroprotective Activity*

The benzylic phloroglucinol-terpene hybrids, melaleucadines A (**7.14**) and B (**7.15**), Table 7 and Figure 14, isolated from the leaves and branches of *M. leucadendron*, exhibited potential neuroprotective effect on the dopaminergic neuron cells (PC12) from cortisone-induced neural damage [12]. Recently, a larger group of benzylic phloroglucinol-terpene hybrids (*Syn*. benzyl phloroglucinol-based meroterpenoids), isolated from the fruits of *M. leucadendron*, Table 7 and Figure 14, has been *in vitro* evaluated for its neuroprotective effect of cortisone-induced neurotoxicity on PC12 cells. The reported results showed that (+)-leumelaleucol A (**7.1**), leumelaleucol B (**7.3**), leumelaleucol D (**7.5**), leumelaleucol E (**7.6**), leumelaleucol F (**7.7**), and leumelaleucol G (**7.8**) increased the survival of treated PC-12 cells with the highest activity attributed to leumelaleucol G and E, respectively [13]. Betulinic acid (**2.26**) isolated from *M. bracteata* showed significant inhibition of acetylcholinesterase activity [72].

### *5.4. Molluscicidal and Antischistosomal Activity*

A moderate biocidal effect of the methanol extract of *M. styphelioides* leaves and the isolated compounds, kaempferol-3-*O*-$\alpha$-rhamnoside **1.12,** pedunculagin **6.21,** and casuarinin **6.4**, has been revealed against *Biomphalaria alexandrina* snails [74].

### *5.5. Immunostimulant Activity*

Hashim et al. (2018) reported that *M. leucadendra* fresh leaf extract significantly increased the phagocytic activity of neutrophils, suggesting that it has an immunostimulant effect [44].

### *5.6. Anticancer Activity*

Antiproliferative activity to cultured mouse T-lymphoma cells by hexane and dichloromethane extracts, as well as eugenitin (**5.14**) from *M. leucadendron* leaves, has been reported [50]. Also, the antiproliferative effect of the triterpenes of *M. ericifolia* leaf extract on malignant mouse +SA mammary epithelial cells has been investigated. A group of isolated 28-norlupanes (Table 3 and Figure 3), such as 28-norlup-20(29)-en-3*β*,17*β*-diol (**1.30**), 28-norlup-20(29)-en-3*β*-hydroxy-17*α*-hydroperoxide (**1.31**), 28-norlup-20(29)-en-3*β*-hydroxy-17*β*-hydroperoxide (**1.32**), and 20*S*-17*β*,29-epoxy-28-norlupan-3*β*-ol (**1.28**), showed higher antiproliferative effect compared to other triterpene derivatives, including ursolaldehyde (**1.10**), ursolic acid (**1.11**), asiatic acid (**1.1**), betulin (**1.24**), betulinaldehyde (**1.25**), betulinic acid (**1.26**), and platanic acid (**1.33**) [7]. The cytotoxicity of *M. leucadendra* leaf extract alongside its isolate, myricetin-3-*O*-β-$^{4}C_{1}$-galactopyranuronoid (**4.24**), has been evaluated against three different tumor cell lines: liver carcinoma cell line (Huh-7), breast cancer (MCF-7), and colon cancer (HCT 116). The results showed that the tested natural products exhibited higher cytotoxic activity towards HCT 116 [44].

### *5.7. Antihistaminic Activity*

The chloroform and methanol extracts of the fruits of *M. leucadendron* strongly inhibited histamine release from rat mast cells. Ursolic acid (**1.11**) from the chloroform extract and two stilbenes, oxyresveratrol (**5.32**) and piceatannol (**5.34**) from the methanol extract, have been isolated as the bioactive compounds [9].

### *5.8. Cardiovascular Activity*

Glycosides from the leaves of *M. quinquenervia* inhibit the vascular contraction in aortic rings of rats [54]. Furthermore, betulinic acid (**1.26**) isolated from *M. bracteata* leaves possesses antithrombotic effect, antiplatelet aggregations, and anticoagulants potential [75].

### *5.9. Hepatoprotective Activity*

The total leaf extract of *M. styphelioides* showed a significant hepatoprotective effect in a $CCl_4$-induced toxicity model in mice. It decreased the levels of AST, ALT, ALP, and MDA and increased the level of GSH and antioxidant enzymes compared to those of the $CCl_4$-treated group. It has restored the liver architecture and reduced the fatty changes, central vein congestion, Kupffer cell hyperplasia, inflammatory infiltration, and necrosis induced by $CCl_4$ [45]. Al-Sayed and Esmat (2016) investigated the *in vitro* hepatoprotective compounds in *M. styphelioides* leaves using the $CCl_4$-challenged HepG2 cell model. Marked hepatoprotections by 1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucose (**6.12**), pedunculagin (**6.21**), tellimagrandin I (**6.29**), and tellimagrandin II (**6.30**), Table 6 and Figure 13, were observed as revealed from decreased AST and ALT levels and increased GSH levels [76]. Praecoxin A (**6.22**), an ellagitannin from the leaves *M. ericifolia*, showed promising hepatoprotective activity in $CCl_4$-induced toxicity in mice, where it decreased the $CCl_4$-induced increase in AST, ALP, ALT, total bilirubin, and malondialdehyde (MDA). Histological results indicated a marked improvement in hepatocyte inflammation, degeneration, cell infiltration, necrosis, and hemorrhage [56].

### *5.10. Antisecretory and Antiulcerogenic Activities*

Adesanwo et al. (2009) investigated the antiulcer and antisecretory effect of the ethyl acetate extract of the stem bark of *M. bracteata* on gastric acid secretion and indomethacin-induced ulceration in albino rats. The results indicated that the tested extract significantly reduced gastric secretion and ulceration. Moreover, the researchers suggested that the presence of betulinic acid (**1.26**) and oleanolic acid (**1.20**) in the extract may account for this antiulcer action [77]. Casuarinin (**6.4**), isolated from *M. leucadendra* leaves, exhibited a gastroprotective effect on ethanol-induced ulceration in rats. The potent gastroprotective effect of casuarinin was shown to be attributed to its anti-inflammatory, antioxidant, and antiapoptotic effects [70].

*5.11. Inhibition of liver microsomal enzyme*

The methanol extract of *M. leucadendron* leaves exhibited strong inhibitory activity on cytochrome P450 2D6 (CYP2D6) [78].

## 6. Conclusions

Natural products have a vital role in pharmaceutical industries. *Melaleuca* species have a diverse metabolic pool of phytochemicals, and their essential oils are commonly used in ayurvedic medicines. Huge amounts of these plants' waste are left behind after the distillation of the essential oils from various species. This review unveiled that melaleuca trees are rich sources of bioactive compounds, including triterpenoids (*e.g.* lupane, nolupane, ursane, and oleanane), flavonoids, and phenolics. Also, a large group of hydrolysable tannins, reported from different *Melaleuca* spp., has been shown to be biologically and pharmacologically active, such as grandinin, pterocarinin, casuarinin, etc. Being a member of the Myrtaceae family, *Melaleuca* spp. are also characterized by the presence of benzylic phloroglucinol-terpene hybrids, which have been reported as neuroprotective compounds. Consequently, with recent technologies in extraction, isolation, and purification and with advancement in biological and pharmacological assay models, this plant waste could participate in new drug discoveries and development.

## Competing Interests

The author has declared that no competing interests exist.

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