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GENUS MELALEUCA: PHYTOCHEMISTRY, PHARMACOLOGY AND EFFECT AGAINST COVID-19

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GENUS MELALEUCA: PHYTOCHEMISTRY, PHARMACOLOGY AND EFFECT AGAINST COVID-19

Abstract

Medicinal plants are used for the prevention and treatment of many diseases as they are rich in phytochemical constituents (like terpenes, flavonoids, and alkaloids) responsible for the pharmacological effects of these plants. Genus Melaleuca named the tea tree, belonging to the family Myrtaceae, is cultivated in Australia as well as in the Pacific and some regions of Asia. It has been employed in Australian traditional medicine for its broad antimicrobial activity because of its contents of phenolic compounds, monoterpenes, tannins, flavonoids, sesquiterpenes, and essential oils. Owing to the valuable uses of plants of genus Melaleuca, for different medical purposes, it was deemed interest to summarize the previous studies reported from 2004 to 2020 in the available literature about the phytochemistry and pharmacological potential of both volatile and non-volatile components of Melaleuca species. Accordingly, this article may help researchers work on plants of genus Melaleuca to promote clinical applications towards the development of novel drugs of diverse pharmacological activities, including inhibitory effects on COVID 19 obtained from Melaleuca species.

Keywords

Melaleuca, phytoconstituents, essential oil, Myrtaceae, polyphenols, pharmacological activities, COVID 19 inhibitory effect

1. INTRODUCTION

Traditional medicine plays a crucial role within the health system of both urban and rural populations due to many reasons: availability, accessibility, cultural and traditional beliefs, and sometimes affordability as per the WHO global report on traditional medicine 2019. Around 80% of the world population use traditional medicine to satisfy their primary healthcare need (Ngbolua, 2018). The pharmacological potential of many plant species is due to the presence of phytochemicals like saponins, glycosides, tannins, alkaloids, flavonoids, terpenes that have played a vital role in the discovery of new pharmaceutical molecules (Batiha et al., 2020). Many research groups have focused on developing synthetic, or semi-synthetic analogs of those phytochemical compounds and this helped to better understand the mechanism of the action of molecules through structure-activity relationship studies with the aim of developing new effective drugs (Tringali, 2020). Myrtaceae family known also as the myrtle present in Queensland, New South Wales, consists of around 3000 species and 140 genera. The family is abundant in Australia but is also distributed in tropical and subtropical regions. Plants of family Myrtaceae are shrubs to big trees. The leaves are opposite, leathery, simple, glandular-dotted, and evergreen. Seeds do not have endosperm. This family is split into two subfamilies Leptospermoideae and Myrtoideae (Ngbolua, 2018). It is one of the most promising plant families, due to its value and pharmacological potential in traditional medicine (Laribi et al., 2020). Genus Melaleuca, named tea trees or paperbark trees, have spiral leaves. Its name, tea tree, is being after the sailor James Cook drunk this herb rather than tea during his journey to Australia in 1770 (Bar, 2020). Melaleuca is a large genus belonging to the Myrtaceae family consisting of 290 species indigenous to New Zealand, Australia, New Guinea, Papua, Indonesia, Solomon Islands, Vietnam, Thailand, Cambodia, Malaysia, and Myanmar. Cultivation of Melaleuca started in Australia then extended to increase the essential oil production. The most favorable habitat is the Coastal region preferably in a moist soil environment and filled with sun. These species are resistant and may support different environmental conditions like drylands, acidic soil, flooded soil, or saline soil, but cannot tolerate extremely low temperatures. Plants of Genus Melaleuca are small trees or tall shrubs that possess spiral leaves that are hairless with glands rich in aromatic oil, and to gather the oil at the time of harvest the entire plant is eradicated from 6 to 18 months. The flowers are in clusters or spike, the flowering begins early at periods and intensity that varies among species. The seeds have a testa with an embryo but without endosperm (Bar, 2020; Brophy et al., 2013; Sharifi-Rad, Salehi, et al., 2017). Melaleuca is familiar as an aromatic medicinal plant because of its beneficial essential oil rich in hydrocarbon and oxygenated monoterpenoids, sesquiterpenes, and phenolic compounds having potent anti-oxidant, anti-inflammatory and antimicrobial effects (Sharifi-Rad, Salehi, et al., 2017). The oil production output is high in some species as M. alternifolia and M. cajuputi and small in others as M. quinquenervia. Large leaves species such as M. cajuputi and M. quinquenervia produce respectively the cajuput oil and niaouli oil. These oils were reported beneficial for many medicinal uses like intestinal problems as worms, toothache, headache, bronchitis, and laryngitis, in addition to its insecticidal effect. Furthermore, the leaves of these plants are used in Australia for fever, congestion, influenza after crushing the leaves and inhaling its vapor. Tea tree oil (TTO) is the oil of terpinen-4-ol type extracted from some Melaleuca species mainly from M. alternifolia. This oil has a strong antimicrobial potential. The tea tree oil is found in many cosmetic products as shampoos, sunscreens, and various skin products for microbial infections. Moreover, the blossom of the genus Melaleuca produces honey of great value (Bar, 2020). It is also utilized in skin infections like scabies, herpes, and acne. Several clinical studies proved the effect of tea tree oil against athlete's foot. Thai traditional medicine showed the potential of Melaleuca alternifolia against acne, and that of Melaleuca alternifolia and M. leucadendron for the treatment of psoriasis in South America. The efficacy of tea tree oil extracted from Melaleuca alternifolia was proved in a comparative study of its effect versus erythromycin and Aloe vera (Mazzarello et al., 2018). Besides the importance of essential oil in Genus Melaleuca, the non –volatile components in this plant are of great value being reported for its antiparasitic, antimicrobial, antioxidant, neuroprotective, anti-inflammatory antihistaminic anticancer, hepatoprotective, antischistosomal activities. The reported articles were done either on the crude extract of the plant or on the isolated compounds among which the anticancer potential that was studied on betulinic acid obtained from the Melaleuca plant and was vital in anti-cancer drug development (Bar, 2020). Taiwan folk medicine has also used the barks and leaves of M. leucadendron as a tranquilizer, sedative, for

pain relief, and for gout treatment in Vietnam. Many other remedies were recorded for the relief of headaches, vertigo, rheumatism, and convulsions in Indonesia. The leaves were proved useful for hyperlipidemia and obesity in Indonesia. In the Philippines and Cuba, this species was evaluated against malaria, dermatitis, respiratory disorders, and inflammation in Senegal folk medicine. M.quinquenervia was reported as a repellant for gastrointestinal disorders in Thai medicine. M.cajuputi was also recorded as an antimicrobial (Sharifi-Rad, Salehi, et al., 2017). Non-volatile components in Melaleuca are mainly terpenoids and phenolic compounds. The plant phenolics are formed of phenylpropanoids, flavonoids, polyphenols, and free phenolic acids. Triterpenoids which are plant metabolites having important pharmacology, are of various skeletons like derivatives of lupine, ursane, and oleanane. This plant is also rich in flavonoids that were highly investigated in literature for their various pharmacological actions. They include flavonols, flavans, and flavones. The dominant group is flavonol and is characterized by the presence of methyl esters. Additionally, several flavonoid glycosides were reported together with glucose, rhamnose, glucuronic acid, and xylose. Hydrolysable tannins with a potent antioxidant effect are also phytochemicals present in the non-volatile part of Melaleuca like oligomeric ellagitannins, gallitannins. Miscellaneous compounds like minor alkaloids, naphthalene were also isolated from the non-volatile parts of Melaleuca (Bar, 2020). This article aims to describe the phytochemistry and the pharmacological importance of both volatile and non-volatile parts of Genus Melaleuca belonging to the family Myrtaceae, in addition, it highlights the structure activity relationships of the most promising species. This manuscript was achieved with the help of google scholar and Pubmed to collect the data published in monographs and articles dated from 2000 to 2020. Phytochemistry of Melaleuca species The previously isolated compounds from different Melaleuca species were identified by GC (Gas Chromatography), HPLC (High-Performance Liquid Chromatography), UV, MS (Mass Spectrometer), and NMR (nuclear magnetic resonance), and are presented in tables 1,2, and 3.

Table 1: A presentation of the most promising Melaleuca species

Melaleuca species	Illustration	Nature of the oil/oil yield	Ref.
M.styphelioides		-Sesquiterpenoid: caryophyllene oxide (22-26%) and staphulenol (18-20%) -small amounts of monoterpenes (α-pinene,1.8cineole, p-cymene) -oil yield is little less than 0.1%	(Al-Sayed et al., 2020; Ferdaous Albouchi et al., 2018; Brophy et al., 2013)
M. alterrnifolia		-Three chemotypes 1- the main commercial chemotype contained terpinen-4-ol. This was accompanied by significant amounts of a-terpinene and g-terpinene. 2- Chemotype II contained 1,8-cineole (25–90%) and associated monoterpenes. 3- Chemotype III contained terpinolene (40–55%) as its principal component. -Oil yield 3-6%	(Brophy et al., 2013; Farag et al., 2004; Sandner et al., 2020)
M.cajuputi		1,8-cineole (15–60%), limonene (1–5%), viridiflorene (0.5–7%), a-terpineol (1–7%), globulol (0.2–8.0%), viridiflorol (0.2–10.0%), spathulenol (0.4–30.0%) and b-caryophyllene (1–4%) Oil yield is 0.4–1.2%.	(Brophy et al., 2013; Bua et al., 2020; Rattanaburi et al., 2013)

M.armillaris		monoterpenes. The principal component was 1,8-cineole (66–73%) Sesquiterpenes contributed little to the oil, with the most prominent members being b-caryophyllene (1–3%), aromadendrene (0.2–2.0%), d-cadinene (0.7–2.0%) and Globulol (0.3–2.0%). -oil yield 0.1–0.3%.	(Brophy et al., 2013; Farag et al., 2004; Siddique et al., 2017)
M.leucadendra		-three chemotypes 1-Chemotype I contained methyl eugenol (94–98%), with insignificant amounts of E-methyl isoeugenol (<1%) 2-Chemotype II contained E-methyl isoeugenol (27–90%, the majority >70%), with lesser amounts of methyl eugenol (6–25%) 3-The western provenances produced an oil (chemotype III) that contained 1,8-cineole (10–45%), p-cymene (5–22%), a-pinene (4–19%), limonene (3–6%) and a-terpineol (trace–9%) The oil yield of the aromatic chemotypes I and II (dry weight, w/w) was 1.0–2.5%, while that from the terpenoid chemotype, chemotype III, was 0.1–0.5%.	(Brophy et al., 2013; Farag et al., 2004)
M.ercifolia		Monoterpenic Chemotypes were not really present but there was a distinct association between oil composition and latitude. The more northerly provenances of this species were rich in linalool, while the more southerly provenances were rich in 1,8-cineole Oil yield 0.8–2.0%	(Brophy et al., 2013; Farag et al., 2004)

Table 2. Chemical composition of the essential oils extracted from the fresh leaves of five *Melaleuca* species (Elmi et al., 2019; Farag et al., 2004)

			Area percentage		
Identified constituents	***M. alternifolia***	***M. ericifolia***	***M. leucadendron***	***M. armillaris***	***M. styphelioides***
***α*-Pinene**	4.4	0.12	4.24	0.02	1.53
(-) Spathulenol	–	–	–	–	9.65
1,8-Cineole	2.15	0.36	64.3	33.93	0.59
1-Dodecen-3-yne	–	–	–	–	3.26
1-Tetradecene	–	–	0.25	–	–
2,4-Dodecadienal	–	–	–	–	0.73
2-Nonenal	–	–	–	–	0.63
3-Decyne	–	–	–	–	1.9
Aromaddendrene	1.38	–	–	–	2.24
Benzaldehyde	–	–	0.29	–	–
Caryophyllene oxide	0.76	–	–	–	43.78

			Area percentage		
Identified constituents	***M. alternifolia***	***M. ericifolia***	***M. leucadendron***	***M. armillaris***	***M. styphelioides***
***cis*-Pinene hydrate**	–	–	–	0.04	–
***cis*-Piperitol**	–	–	–	0.14	–
D-Elemene	–	–	–	0.21	–
D-Germacrene	–	–	–	0.24	–
Elemicin	–	0.08	–	–	–
Estragol	–	0.26	–	–	–
Eugenol	–	0.07	–	0.09	–
Geraniol	–	–	–	0.06	–
Ledol	–	–	1.2	–	2.82
Limonene	1.78	–	6.7	2.61	–
Linalool	–	–	0.1	0.67	–
Methyl eugenol	–	96.84	–	–	–
Sabinene	0.03	–	–	6.59	–
***tans*-pinene hydrate**	–	–	0.16	0.43	–
Terpinen-4-ol	41.49	–	0.82	18.79	2.39
Terpinolene	3.18	–	0.16	2.03	–
Terpinyl acetate	–	–	–	3.09	–
***trans* Alpha-dehydroterpineol**	–	–	–	0.28	–
Valencene	–	–	3.91	–	–
***α*-Cadinene**	–	–	–	0.29	–
***α*-Eudesmol**	–	–	0.15	–	–
***α*-Terpinene**	9.59	–	–	5.8	–
***α*-Terpineol**	4.42	–	11.02	3.49	1
***α*-Thujene**	–	–	–	1.52	–
***β* -Eudesmol**	–	–	0.17	–	–
***β* -germacrene**	–	–	–	0.29	–
***β* -Myrcene**	0.72	–	0.65	2.28	–
***β* -Pinene**	0.03	0.17	1.67	1.35	–
***γ* -Elemene**	–	0.28	–	–	–
***γ* -Terpinene**	20.55	–	0.57	10.37	0.61
***γ* -Terpineol**	–	–	0.25	–	–
***ρ* -Cymene**	3.66	–	0.3	0.59	0.83

Table 3. Flavonoids isolated previously from the genus *Melaleuca*

Compound	Name	Plant/Part	Reference
1	Apigenin	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
2	Apigenin-7-methyl ether		
3	Apigenin-7,4`-dimethyl ether		
4	Herbacetin-3-O-glucuronide	Leaves of *M. squarrosa*	(Bar, 2020)
5	5-Hydroxy-7,4`-dimethoxy-6,8-dimethylflavone	Leaves of *M. cajuputi*	(Rattanaburi et al., 2013)
6	Kaempferol	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
		Leaves of *M. leucadendron*	(Bar, 2020)
		Leaf and stem of *M. quinquenervia*	(Goetz & France, 2012)
		Leaves of *M. ericifolia*	(Bar, 2020)
7	Kaempferol-3-methyl ether	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
8	Kaempferol-3,7-dimethyl ether	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
9	Kaempferol-3,7,4`-trimethyl ether	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
10	Kaempferol-3-O-glucoside	Leaves of *M. leucadendra*	(Bar, 2020)
11	Kaempferol-3-O-xylosyl-(1```→2``) -glucoside	Leaves of *M. ericifolia*	(Bar, 2020)
12	Kaempferol -3-O-rhamnoside	Leaves of *M. ericifolia*	(Bar, 2020)
		Leaves of *M. styphelioides*	(Al-Sayed, El-Lakkany, et al., 2014)
13	Kaempferol-3-O-(2``-O-galloyl)-glucuronide	Leaves of *M. squarrosa*	(Bar, 2020)
14	Luteolin	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
		Honey of *M. quinquenervia*	(Bar, 2020)
15	Luteolin-7,3`-dimethyl ether	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
16	Miquelianin	Leaves of *M. leucadendra*	(Bar, 2020)
17	Myricetin	Leaves of *M. leucadendra*	(Bar, 2020)
18	Myricetin 3-O-(2``-O-galloyl)-α-rhamnopyranoside	Leaves of *M. quinquenervia*	(Bar, 2020)
19	Myricitrin	Leaves of *M. leucadendra*	(Bar, 2020)
		Leaves of *M. ericifolia*	(Bar, 2020)
20	Myricetin 3-O-β-D-glucoside	Leaves of *M. quinquenervia*	(Bar, 2020)
		Leaves of *M. leucadendra*	(Hashim et al., 2018)
21	Myricetin 3-O-β-D-glucuronide	Leaves of *M. quinquenervia*	(Bar, 2020)
22	Myricetin 3-O-rhamnoside	Leaves of *M. leucadendra*	(Hashim et al., 2018)
23	Myricetin 3-rutinoside	Leaves of *M. leucadendra*	(Hashim et al., 2018)

Compound	Name	Plant/Part	Reference
24	Myricetin-3-O-β-4C1-galactopyranuronoid	Leaves of *M. leucadendra*	(Hashim et al., 2018)
25	Myricetin 3-O-xylosyl-(1```→2``)-glucoside	Leaves of *M. ericifolia*	(Bar, 2020)
26	Quercetin	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
		Leaves of *M. leucadendra*	(Hashim et al., 2018)
		Leaf and stem of *M. quinquenervia*	(Bar, 2020)
		Leaves of *M. ericifolia*	(Bar, 2020)
27	Quercetin-3-methyl ether	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
28	Quercetin-3,7-dimethyl ether	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
29	Quercetin-3,7,3`-trimethyl ether	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
30	Quercetin-3,7,4`-trimethyl ether	Leaves of *M. huegelii*	(Wollenweber et al., 2000)
31	Quercetin-3-O-xyloglucoside	Leaves of *M. leucadendra*	(Hashim et al., 2018)
32	Quercetin	Leaves of *M. leucadendra*	(Hashim et al., 2018)
		Leaf and stem of *M. quinquenervia*	(Bar, 2020)
		Leaves of *M. ericifolia*	(Bar, 2020)
		Leaves of *M. cajuputi*	(Rattanaburi et al., 2013)
33	Quercetin-7-O-(6``-galloyl) -β-D-glucopyranoside	Leaves of *M. quinquenervia*	(Bar, 2020)
34	Quercetin-3-O-xylosyl-(1```→2``) -glucoside	Leaves of *M. ericifolia*	(Bar, 2020)
35	Quercetin-3-O-galactoside	Leaves of *M. ericifolia*	(Bar, 2020)
36	Quercetin-3-O-glucoside	Leaves of *M. ericifolia*	(Bar, 2020)
37	Quercetin-3-rutinoside, rutin	Leaves of *M. leucadendra*	(Hashim et al., 2018)
38	5,7,3`,4`-Tetrahydroxyflavone 2`-O-β-D-glucuronide	Leaves of *M. quinquenervia*	(Bar, 2020)
39	Tricetin	Leaves of *M. ericifolia*	(Bar, 2020)
		Leaves of *M. leucadendra*	(Hashim et al., 2018)
		Honey of *M. quinquenervia*	(Bar, 2020)
40	Catechin	Leaves of *M. leucadendra*	(Hashim et al., 2018)

Compound	Name	Plant/Part	Reference
41	Kryptostrobin	flowers of *M. quinquenervia*	(Bar, 2020)
42	Leucadenone A	Leaves of *M. leucadendra*	(Bar, 2020)
43	Leucadenone B	Leaves of *M. leucadendra*	(Bar, 2020)
44	Leucadenone C	Leaves of *M. leucadendra*	(Bar, 2020)
45	Leucadenone D	Leaves of *M. leucadendra*	(Bar, 2020)
46	Melanervin	Flowers of *M. quinquenervia*	(Bar, 2020)
47	Strobopinin	Flowers of *M. quinquenervia*	(Bar, 2020)

This literature review on the phytochemistry of genus *Melaleuca* revealed the presence of 47 flavonoids, 30 hydrolysable tannins, a variety of other phenolic compounds, and triterpenoids in the non-volatile part of *Melaleuca* in addition to many active constituents in the essential oil mainly sesquiterpenes (oxygenated sesquiterpenes as Globulol, viridiflorol) ,sesquiterpene hydrocarbons as aromadendrene, δ-cadinene), monoterpenes (oxygenated monoterpenes as terpineol, 1.8 cineole) and monoterpene hydrocarbons as (sabinene, limonene, p-cymene), phenolics such as (eugenol). Oxygenated monoterpenes also referred to as terpenes and oxygenated sesquiterpenes are referred to as terpenoids(Sharifi-Rad, Sureda, et al., 2017). These phytochemical constituents are responsible for the diversity in the pharmacological potential of *Melaleuca.*

2. PHARMACOLOGICAL ACTIVITIES

2.1 Antimicrobial Potential

The literature survey showed a broad antimicrobial potential of *Melaleuca*, some species are antibacterial, others are potent antiviral or antifungal. The antifungal potential of *Melaleuca* was reported in a study that compared the in vitro antifungal effect between volatile and non-volatile extracts of *Melaleuca styphelioides* leaves and the activity was proven against *Penicillium digitatum, Rhizopus nigricans, and Aspergillus niger*. around 10 components of the oil were isolated with eugenol the principal one (87,2%). The analysis was done using Gas Chromatography (GC). The samples tested have shown a difference within the level of selectivity of the microorganisms, the leaves oil was potent against *A.niger*, and also the most susceptible species for the aqueous extract was *P.digitatum* (IC50=9,54 mg/ml) while *R.nigricans* was the foremost vulnerable to the methanolic extract(IC50=8,31mg/ml) therefore the volatile oil, methanolic and aqueous extracts of *Melaleuca styphelioids* leaves have antifungal potential thus it is often used as an alternative to chemical preservatives in food and pharmaceutical industries (Bar, 2020; Laribi et al., 2020).

Another study was done on the oil of *Melaleuca styphelioides* in vitro on eight selected microorganisms by the assay of both MBC (Minimal Bactericidal Concentration) and MIC (Minimum Inhibitory Concentration) and also the broth dilution method, the results showed high antimicrobial activity for the oil against *S. epidermidis*(Sharifi-Rad, Salehi, et al., 2017) In conclusion, different *Melaleuca* species showed a potential antimicrobial activity such as *M.ercifolia* and *M.leucadendron* against *Aspergillus niger* and *Bacillus subtitles* and a strong antiviral potential (Farag et al., 2004).*M alternifolia* activity was proved against Tobacco mosaic virus in Nicotiana glutinosa (Farag et al., 2004), in addition to a potential against various bacteria and fungus such as *S. aureus* and *E. coli, S. mutans, L. monocytogenes, Porphyromonas gingival, Porphyromonas endodontalis, Pseudomonas aeruginosa, Candida albicans, Aspergillus niger, and Candida glabrata* (Cordeiro et al., 2020; Wińska et al., 2019).

Other *Melaleuca* species such as *M.Linarrifolia, M. fulgens, M. alternifolia, M. armillaris and M. bracteata* showed a broad-spectrum antibacterial effect against gram positive and gram -negative bacteria (Li et al., 2018; Padalia et al., 2015; Siddique et al., 2017).*M. leucadendra* showed also a wide potential against *Leishmania amazonensis, Trypanosoma brucei, Microsporum canis, Plasmodium falciparum, Trypanosoma cruzi, Leishmania infantum, T. brucei. parapsilosis, E. faecalis, S. aureus, M. canis, P. aeruginosa, E. coli, M. canis, C. albicans* (Bautista-Silva et al., 2020; Zhang et al., 2019).

2.2 Antioxidant and Anti-Inflammatory Activities

The antioxidant effect was reported in articles that proved the antioxidant potential of methanolic extract of leaves of *Melaleuca styphelioides* using FRAP, DPPH, ABTS+ assays, pro-inflammatory mediators like nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), nuclear factor kappa B, and intercellular adhesion molecule-1 in interferon-gamma/histamine inflammation-induced human NCTC 2544 keratinocytes. The analysis was done by LC/MS-MS technique to spot and quantify the components and by Western blot and RT-PCR to assess the anti-inflammatory potential. The results showed that the methanolic extract has the best level of phenols like ellagic acid, quercetin, so it has a strong anti-inflammatory and antioxidant potential, it's also beneficial for the treatment of inflammatory skin diseases (Ferdaous Albouchi et al., 2018)

Further assays performed on ellagitannins isolated from *Melaleuca styphelioides* by the generation of f/MLF/CB induced anion and also the release of elastase by human neutrophils, the results showed a powerful antioxidant effect and also a heme reducing property that may be helpful within the development of heme reducing drugs, additionally to the reduction in elastase release by 90,2% which reflects a high anti-inflammatory effect by direct inhibition of inflammatory enzyme activity(Al-Sayed et al., 2020) Moreover, one among the reported studies that isolated pedunculagin, tellimagradinI, pterocarinin A, and casuarinin from *Melaleuca* styphelioides leaves, the compounds were identified by 1D and 2D NMR, HRESI-MS/MS, and UV data. The study aimed to demonstrate the renoprotective activity of the isolated compounds in glucose and oxalate challenged NRK-49F cell model, the evaluation of the isolated constituent's antioxidant effect was done on the idea of their effect on lipid peroxidation levels and antioxidant enzymes activities. The results showed potential antioxidant and cytoprotective properties in oxidative stress-mediated kidney damage, additionally, the phenolic compounds demonstrated a nephroprotective role in urinary diseases and diabetes mellitus (Ganesan et al., 2018).

2.3 Anti-Allergic Effects

The anti-allergic potential was studied on ellagitannin isolated from *Melaleuca styphelioides* using MTT viability assay, ellagitannin reduced the viability of rat basophilic leukemia cells by 31,3% and suppressed 20,3% of β-hexosaminidase induced with calcium ionophore so it was proved to possess anti-allergic activity at a level of 10µM (Al-Sayed et al., 2020).

2.4 Hepatoprotective Potential

The synergistic antioxidant, hepatoprotective potential was also measured on methanolic extract of *Melaleuca styphelioides* leaves in CCL4 induced liver injury in mice, using DPPH radical scavenging assay and monitoring the level of antioxidant enzymes (GST, SOD, GR, and GPx) additionally to the level of AST, ALT, ALP within the serum and levels of SOD (superoxide dismutase), GSH (glutathione), GPx (glutathione peroxidase), GR (glutathione reductase), GST (glutathione S transferase) and MDA (malondialdehyde) in liver homogenate. Identification of MSE was done by UV, NMR, and HRESI-MS/MS data. The results showed that the MSE (*M.styphelioides* extract) increased the antioxidant enzymes and GSH (glutathione) levels (29 and 57%) compared with the CCL4-treated groups, histological results showed improvement within the status of the liver, in cell degeneration necrosis and cell infiltration(Al-Sayed, El-Lakkany, et al., 2014) further article showed that the hepatoprotective potential of the methanolic extract of *Melaleuca styphelioides* was mainly attributed to tellimagrandin I,II, pentagalloyl glucose and pedunculagin in an in-vitro study in CCL4-challenged HepG2 cell model(Al-Sayed & Esmat, 2016). More studies were done to evaluate the hepatoprotective and antioxidant potential on the ellagitannin isolated from the methanolic extract of *Melaleuca styphelioides*

by measuring ALT (alanine aminotransferase) and AST (aspartate aminotransferase) in a culture of HepG2 cells challenged with CCL4, the subsequent parameters were evaluated MDA, GSH, SOD for hepatoprotective effect and also the DPPH radical scavenging assay for antioxidant activity measurement. Results demonstrated a decrease in ALT, AST levels, and a rise in antioxidant enzymes, so *Melaleuca styphelioides* contains hepatoprotective components like silymarin, ellagitannin, and its derivative rhoipteleanin H a potent anti-elastase agent thus this may be promising within the development of medicine for elastase-related inflammatory conditions (Al-Sayed et al., 2020).

2.5 Molluscicidal and Antischistosomal Activity

The biocidal effect was proved on the isolated compounds pedunculagin, casuarinin, kaempferol-3-O- α –rhamnoside from the methanolic extract of *Melaleuca styphelioides* leaves, the structure of the isolates was detected by 1D and 2D NMR, HRESI –MS/MS data and Ultra-Violet spectroscopy these compounds showed a moderate biocidal effect against *Biomphalaria Alexandrina* snails in several stages of the life cycle so this is often very promising within the discovery of antischistosomal drugs within the future(Al-Sayed, Hamid, et al., 2014)

2.6 Anti-Acanthamoeba effect

The antiparasitic potential of the subsequent isolated components isolated from the volatile oil extracted of the *Melaleuca styphelioides* leaves which were identified by gas chromatography-mass spectrometry (GC-MS) :Caryophyllene oxide (23,42%), Ledol (5,98%), Isoaromadandrene epoxide (7,45%), Spathulenol (20,5%), Isopinocarveol(2,18%) and α -pinene(3,82%).The data showed that the oil may be a potent anti-amoeba since it inhibits the expansion of *Acanthamoeba castellanii* Neff by an IC50 of 69,03+9,17µg/ml, but this was proven in vitro only so further studies on the toxicity of volatile oil on human macrophages and in vivo studies are needed (Ferdaous Albouchi et al., 2017).

2.7 Aphidicidal Activities

A reported study was done on the oil of *M.styphelioides* against insect pests, *Aphis gossipi*, *Myzus persicae*, and *Aphis spiraecola* infecting citrus trees.GC/MS was used to determine the oil chemical composition and therefore the following components were identified staphulenol (20,5%) and caryophyllene oxide(23,42%), isoaromadendrene epoxide (7,45%),isopenocarveol (2,18%), ledol (5,98%) and α-pinene (3,82%).The results showed a potent fumigant and cell toxicity against the pest species so it may be helpful in the development of recent strategies for agriculture production to use of *M.styphelioides* oil as fumigant insecticide against citrus aphids adults and nymphs(F. Albouchi et al., 2018; Ikbal & Pavela, 2019)

2.8 Chemosensitizing Properties

A study evaluated the chemosensitizating effect of CRYO which is a sesquiterpene isolated from the essential oil of *M. styphelioide*s, the results showed the benefit from using CRYO at non-toxic dose together with sorafenib since it increases the intracellular accumulation of the drug in hepatocellular cancer cells. So, this phytochemical proved a potential to improve synergistically the cytotoxic power of chemotherapeutic medicines(Di Giacomo et al., 2019).

2.9 Inhibitory Activity against COVID-19

Moreover, the great interest in *Melaleuca* pushed 15 authors to evaluate the inhibitory effect of *M. cajuputi* oil against COVID-19 by docking stimulation technique. They proved that the following active components in the essential oil have an anticoronavirus potential in the following order Terpineol (TA2), Guaiol (TA5), Linalool (TA19), Cineol (TA1), βSelinenol (TA3), α-Eudesmol (TA4), γ-Eudesmol (TA7). These phytochemicals attack synergistically the PDB6LU7 protein found in the SARS-COV-2 and inhibit its host receptor the ACE2 protein so, the authors concluded that this oil is beneficial in the prevention of COVID-19 spread (My et al., 2020).

Some other pharmacological activities of different *Melaleuca* species are summarized in table 4

Table 4: Pharmacological potential of some *Melaleuca* species

***Melaleuca* species**	**Isolates**	**References**
I-Antioxidant and anti-inflammatory		
M.stypheliodes	Leaves extract: Phenols (like ellagic acid, quercetin) Ellagitannins, pedunculagin, tellimagradinI, pterocarinin A, and casuarinin	(Al-Sayed et al., 2020; Ferdaous Albouchi et al., 2018; Ganesan et al., 2018)
M. leucadendron	Essential oil : eugenol methyl ether	(Siddique et al., 2020)
M. fulgens	Essential oil: eugenol methyl ether	(Siddique et al., 2020)
M. bracteata	Essential oil: eugenol methyl ether	(Li et al., 2018; Siddique et al., 2020)
M.armillaris	Essential oil : eugenol methyl ether	(Chabir et al., 2011; Siddique et al., 2017)
M. cajuputi	Leaves and barks: β-triketone flavanone hybrids, cajuputones A–C (1–3)	(Xu et al., 2020)
M.squarrosa	Ellagitannins : squarrosanins A, B, and C Flavonoïdes : kaempferol-3-O-(2-O-galloyl) - glucuronide, herbacetin-3-O-glucuronide C-glucosidic tannins	(Yoshimura et al., 2008)
M. quinquenervia	Niaouli essential oil	(Goetz & France, 2012)
M.leucadendra	Ethanolic extract of Leaves: myricetin 3-O-β-4 C1 -galactopyranuronoid	(Hashim et al., 2018)
II-Anti-malarial		
M.armillaris	Essential oil	(Chabir et al., 2011)
III- Cytotoxic, anti-tumor		
M.armillaris	Essential oil	(Chabir et al., 2011)
M. alternifolia	Tea tree oil	(Ali et al., 2015)
M.leucadendra	-Ethanolic extract of Leaves: myricetin 3-O-β-4 C1 -galactopyranuronoid -Essential oil (1,8-cineole)	(Hashim et al., 2018; Monzote et al., 2020)
IV- Immunomodulator		
M.alternifolia	TTO (terpinene-4-ol)	(Sandner et al., 2020)
M. quinquenervia	Niaouli essential oil (1,8 cineole)	(Goetz & France, 2012)
V-Antimycobacterial (tuberculosis)		
M. cajuputi	Essential oil	(Bua et al., 2020)
VI-Anti-Herpes virus		
M. quinquenervia	Niaouli essential oil	(Goetz & France, 2012)
M. styphelioides	Tellimagrandin I	(Treml et al., 2020)
VII- Leshmanicidal		
M.leucadendra	Essential oil (1,8-cineole)	(Monzote et al., 2020)

3. DISCUSSION

The literature review on the pharmacology and phytochemistry of genus Melaleuca and discussed previously revealed the potent antimicrobial effects of some species mainly M. alternifolia which oil Tea tree oil (TTO) was reported in dermatologic and oral hygiene products for its antimicrobial potential. But references showed that for minimum skin irritation, (TTO) should contain a maximum of 15% cineol and a minimum of 30% terpineol(Wińska et al., 2019). Furthermore, the most important species M. alternifolia was incorporated in many novel techniques to benefit from its valuable oil (TTO), in addition to being granted patency for the invention of William John Courtney, who invented a mixture of antimicrobial oils from M. alternifolia and Leptospermum Scoparium (Singh et al., 2009). Besides the TTO and its derivatives were also given the following patency EP1787652, US0195998, US0158127 for their antimycotic potential (Shahid, 2016). Recently, to benefit from the therapeutic activities of this most promising oil, and preventing its degradation by physicochemical processes, a new technique of delivery for terpinen-4-ol the major component of TTO was adopted. It consists of liposomal formulations incorporated in biomaterials, these new drug delivery systems are more thermostable than the oil itself and exerts better effect (de Assis et al., 2020).Moreover Guanquan Lin prepared TTO microspheres using styrene and butyl methacrylate monomers, with the help of divinyl benzene as a crosslinking agent. This technique resulted in an increase in TTO stability and improvement in its antibacterial effect (Lin et al., 2018).

The articles showed also that terpenoids present in most of Melaleuca species such as M. styphelioides, M. Linarrifolia, M. fulgens, M. armillaris and M. bracteata proved very effective against a large range of Gram-positive and Gram-negative bacteria, fungi, yeast. Thus, further clinical studies are needed to prove that Genus Melaleuca is incredibly a promising plant within the study of microbial resistance.

Each of the above-discussed pharmacological activities is related to a special bioactive component in the Melaleuca species and specifically to the chemical structure or a specific ligand. The structure activities relationship studies done, showed that the antimicrobial effect is related mainly to the Phenolic -OH in the phytochemicals of the essential oil and hydrophobicity of aromatic ring structure that contributes to the penetration and damaging of the microbe plasma membrane(Konuk & Ergüden, 2020). Moreover, the inhibitory potential of M. cajuputi against COVID-19 as assumed by the author is due to the phenolic OH in sesquiterpenes and monoterpenes of the oil such as terpineol, guaiol, linalool, β-Selinenol, α-Eudesmol, and γ-Eudesmol that bind to the amino acid in the PDB6LU7 protein in theSARS-CoV-2 (My et al., 2020). So, advanced studies on this species are necessary to validate the inhibitory effect of M. cajuputi against COVID-19 as well as the possibility of performing clinical studies on novel molecules having the same ligand to prove this pharmacological effect.

Besides, the antioxidant potential is the result of structure-activity relationship such as the antioxidant activities of Squarrosanin, A, B, and C tannins in M. squarrosa that may depend on the conformation of the hydroxyl group at C-1 of the open ring d-glucose making the C-glucosidic tannins more potent as radical scavengers than flavonoids (Kaneshima et al., 2016; Yoshimura et al., 2008). Moreover, the presence of strongly activated methylene groups in the monoterpene hydrocarbons present in the essential oil of some Melaleuca species is responsible for their antioxidant potential such as α-terpinene, terpinolene and γ -Terpinene present in M. armillaris (Chabir et al., 2011).

In addition, the cytotoxicity of M.leucadendra is mainly related to C2-C3-double bond, aromatic ring-B at C-2, and hydroxy groups in ring-B in myricetin 3-O-β-4 C1 -galactopyranuronoid present which is a novel flavonol glycoside isolated from this Melaleuca species.(Hashim et al., 2018; Semwal et al., 2016)

Hopefully, based on the promising results collected in our manuscript, the phytochemicals isolated from Melaleuca, may be the cornerstone in the area of clinical studies that should be done on medicinal plants in parallel with adequate toxicity studies to guarantee the discovery of novel safe and effective drugs.

4. CONCLUSION

This review has been done for the first time on both volatile and non-volatile parts of plants of genus Melaleuca. This work showed that this genus is rich in bioactive compounds mainly sesquiterpenes, flavonoids, triterpenoids, phenols, and hydrolysable tannins, and might be a target in drug manufacturing and development for the treatment of various diseases. Since most of the studies were performed in vitro, further human trials on the phytoconstituents isolated versus placebo are needed to validate the previous findings. Additional efforts are needed to incorporate these bioactive compounds in the pharmaceutical industry and to widen the public understanding of fruits and vegetable consumption containing them to benefit from their potentials in preventing and treating hypertension, cancer, diabetes, and cardiovascular diseases. Moreover, the structure-activity relationship studies showed the importance of the phenolic OH- in the chemical structure of most of the bioactive compounds in many Melaleuca species and this ligand is responsible for the antiviral, antibacterial, antifungal, antioxidant, anti-inflammatory, and anti-leishmania potential of the most promising species such as M. cajuputi, M. alternifolia, M. leucadendron, M. styphelioides, M. squarrosa, M. armillaris, M. ercifolia, M. Linarrifolia, M. bracteata, and M. fulgens.

Based on the results collected from the quantitative characteristics of Melaleuca constituents it is possible to conclude the potent antimicrobial effect of Melaleuca extracts, so this plant can help in the development of new antimicrobial molecules, and in the strategies adopted to counteract the dangerous consequences of antibiotic resistance. But further researches are needed to check its efficacy versus chemical drugs like the antimicrobial effect of the volatile oil extracted versus antibiotics and more phytochemical studies are required in the future to determine the exact mechanism of action and the structure-activity relation-ship of its diverse bioactive constituents. Regulatory authorities within the world need to put more regulatory policies on herbal medicines to assure the safety of those products since the conception about the safety of herbal drugs has to be confirmed by further efficacy and toxicity studies.

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