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Macadamia Genus: An Updated Review of Phytochemical Compounds and Pharmacological Activities

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Abstract: The Macadamia genus of the *Proteaceae* family, which can be found mainly in the southern hemisphere, has many benefits in some disease treatments. Phytochemical compounds and pharmacological activities of this genus were comprehensively reviewed in this article. This article was written by collecting and reviewing a minimum of 50 scientific articles in PubMed, Google Scholar, Science Direct, Elsevier, and PubChem that contain the phytochemical compounds and pharmacological activities of the Macadamia genus. The articles were published in the last 15 years, a minimum of 20 articles in the last 2 years, and they also must have a DOI. The phytochemical compounds that comprised of flavonoid, proanthocyanidin, and other polyphenols compounds. These phytochemical compounds can promote a wide range of pharmacological activities such as antioxidant, anti-inflammatory, anti-dyslipidemia, dietary controlled, antimicrobial, chemopreventive, and NAFLD prevention. Nevertheless, many investigations on phytochemical compounds and pharmacological activities only focussed on a few parts of a plant, especially nuts. Therefore, further research is needed to determine the other parts of Macadamia genus plants' potential chemical compounds and pharmacological activities.

Keywords: Macadamia genus; pharmacological activities; phytochemical compounds.

1. Introduction

The *Proteaceae* family consists of 80 genera and 1800 species widespread in the southern hemisphere [1]. *Proteaceae* family grows well in poor-phosphorus soil and has a low-temperature area (7 °C - 14 °C), especially in South Western Australia and South Africa [2]. The Macadamia genus is composed of four species, including *Macadamia integrifolia* Maiden and Betcher, *Macadamia jansenii* C.L. Gross and P.H. Weston, *Macadamia ternifolia* F. Muell, and *Macadamia tetraphylla* L.A.S. Johnson [3].

Macadamia flowers has around 15 mm long, with one another attached by a short filament to each of four petal-like perianth segments [4]. The fruit of macadamia is identified as a follicle, and it has dark green pericarp color. The part of kernel and nut in the shell as the complete seed is described as a nut. Macadamia kernels consist of two large cotyledons covered by a single layer of epidermal cells [5]. The macadamia tree produces a high-value kernel and oil. Macadamia was harvested 5-6 years after planting [6].

Among four species, only two species produce edible nuts, including *Macadamia integrifolia* and *Macadamia tetraphylla*, of which the species most commonly grown for its nuts is *Macadamia intergrifolia* [7]. Those species of the Macadamia genus are evaluated for active compounds and pharmacological activities.

2. Materials and Methods

This article was written by collecting and reviewing scientific articles that contain the phytochemical compounds and pharmacological activities of the Macadamia genus. Those articles had been published in the last 15 years, including a minimum of 20 articles in the last 2 years. The articles were presented in PubMed, Google Scholar, Science Direct, Elsevier, and PubChem, which also must have a DOI.

3. Results and Discussion

3.1. Phytochemical compounds of Macadamia genus.

Macadamia integrifolia and *Macadamia tetraphylla* produced macadamia oil that contains monounsaturated fatty acids (75%), where oleic acid being the highest, followed by palmitoleic acid and eicosenoic acid. Saturated fatty acids (15%) and polyunsaturated fatty acids (10%) are also presented in macadamia oil. High concentrations of palmitoleic acid are determined in macadamia nuts (15–22%) [8]. Hu *et al.* (2019) stated that palmitoleic acid affected health as well as its association with various diseases, such as obesity, cardiovascular disease, Non-alcoholic Fatty Liver Disease (NAFLD), and Non-alcoholic Steatohepatitis (NASH), diabetes and insulin resistance, also cancer. In previous studies, palmitoleic acid could decrease diabetes, inflammation, and cardiovascular diseases [9].

The chemical compounds in macadamia nut such as sterol, tocopherol, squalene, and total phenolic content were increased by roasting. Meanwhile, tocopherol and thiamine were decreased by roasting. The total polyphenol content increased 25.6%, and the oxidative stability index of kernels increased 21.6% [10].

The previous studies exposed that the Macadamia genus could produce some secondary metabolites, as shown in Table 1.

Table 1. Phytochemical compounds in Macadamia genus.

Macadamia species	Plant part	Compounds	Ref
M. integrifolia	Leaves	Vit.E, minerals (K, Ca, Na, Fe, Cu), flavonoids, tannins	[11,12]
	Kernel	Vit.E, minerals (K, Ca, Na, Fe, Cu)	[11]
	Pericarp	Vit.E, minerals (K, Ca, Na, Fe, Cu)	[11]
	Flowers	Flavonoids, tannins	[12]
	Nut	Proanthocyanidins, phenolic acids, phytates, lipids (myristic, palmitic, palmitoleic, oleic, linoleic, stearic, elaidic, arachidic, eicosenoic), minerals (Na, Al, B, Ca, Cu, Fe, K, Mg, Mn, Na, P, S, Zn),	[13,14]
	Oil	Lipids (lauric, myristic, palmitic, palmitoleic, margaric, isomargaric, heptadecanoic, heptadecenoic, stearic, arachidic, oleic, trans-vaccenic, linoleic, α-linolenic, gadoleic, behenic, cetoleic, arachidonic, erucic), minerals (Na, Mg, K, Ca, Zn, Fe, P, F), amino acids (alanine, glycine, valine, leucine, isoleucine, proline, cysteine, methionine, phenylalanine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, histidine), apigenin 7-glucoside, luteolin, caffeic acid, *p*-hydroxybenzoic acid, squalene, α-tocopherol, γ-tocopherol, α-tocotrienol, γ-tocotrienol, δ- tocotrienol	[8,15-20]

Macadamia species	Plant part	Compounds	Ref
M. tetraphylla	Oil	Lipids (lauric, myristic, palmitic, palmitoleic, stearic, arachidic, oleic, linoleic, α-linolenic, gadoleic, behenic, cetoleic)	[8]
	Skin	Flavonoids, proanthocyanidins	[7]
***Macadamia* sp.**	Nut	Flavonoids, proanthocyanidins, phytosterols (campesterol, clerosterol, β-sitosterol, campestanol, Δ^5-avenasterol + β-sitostanol, $\Delta^{5,24(25)}$-stigmastadienol, Δ^7-stigmastenol, 24-methylenecycloartenol, citrostadienol), amino acids (alanine, glycine, valine, leucine, isoleucine, proline, cysteine, methionine, phenylalanine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, histidine), lipids (lauric, myristic, palmitic, stearic, arachidic, behenic, palmitoleic, oleic, gadoleic, linoleic, α-linolenic), minerals (Fe, Zn, Cu, As, Ca, Cr, Mg, Mn, K, Na, P), proteins (serotonin, legumins, vicilins, and 2S albumins), polyphenols, catechin, epicatechin, γ-tocopherol, α-tocotrienol, γ-tocotrienol, glucose, fructose, sucrose	[21-30]
	Hard shell	2,6-dihydroxybenzoic acid, 3,5-dimethoxy-4-hydroxycinnamic acid	[31]
	Oil	Tocols, phytosterols, lipids (myristic, behenic, lauric, palmitic, palmitoleic, margaric, stearic, elaidic, oleic, linoleic, linolenic, arachidic, gonodic, EPA, behenoic, erucic, DHA, lignoceric), amino acids (lysine, methionine, threonine, tryptophan, phenylalanine, histidine, valine, isoleucine, leucine, arginine, cysteine, proline, glutamic acid, tyrosine, serine), polysaccharides (cellulose, glucose, xylose, arabinose, galactose, mannose, rhamnose, fucose)	[13,32,33]

3.2. Pharmacological activities of Macadamia genus.

3.2.1. Antioxidant activity.

Macadamia nuts (kernel and skin) revealed antioxidant activity in various studies due to their rich-total phenolic content. Extraction of *M. tetraphylla* skin using a mixture of acetone - water (1:1) as a solvent and optimized by ultrasonic extraction showed antioxidant potential in ABTS (2,2'azino-bis (3-ethylbenzethiazoline-6-sulfonic acid), DPPH (2,2 diphenyl-1-picrylhidrazyl), CUPRAC (Cupric Ion Reducing Antioxidant Capacity), and FRAP (Ferric Reducing Antioxidant Power) methods with the value were 102.36 µM TE/g, 1128.76 µM Trolox Equivalent (TE)/g, 2736.31 µM TE/g, and 1607.82 µM TE/g, respectively [34].

Phytochemical extract of Macadamia nut had EC_{50} 13.4 µmol vitamin C equivalent/g sample using TOSC (Total Oxyradical Scavenging Capacity) method [35]. Furthermore, Macadamia nut's methanol extracts' antioxidant efficacy had IC_{50} values 3 µm and 4.1 µm for raw nut and roasted nut, respectively [36]. Research by Garg *et al.* (2007) demonstrated that plasma levels of 8-isoprostane (a reliable in vivo marker of oxidative stress) were reduced by 18.9% after macadamia nut intervention [37]. The other research by Vadivel *et al.* (2012) mentioned that diet macadamia nuts given by single feeding would improve oxidation status [38].

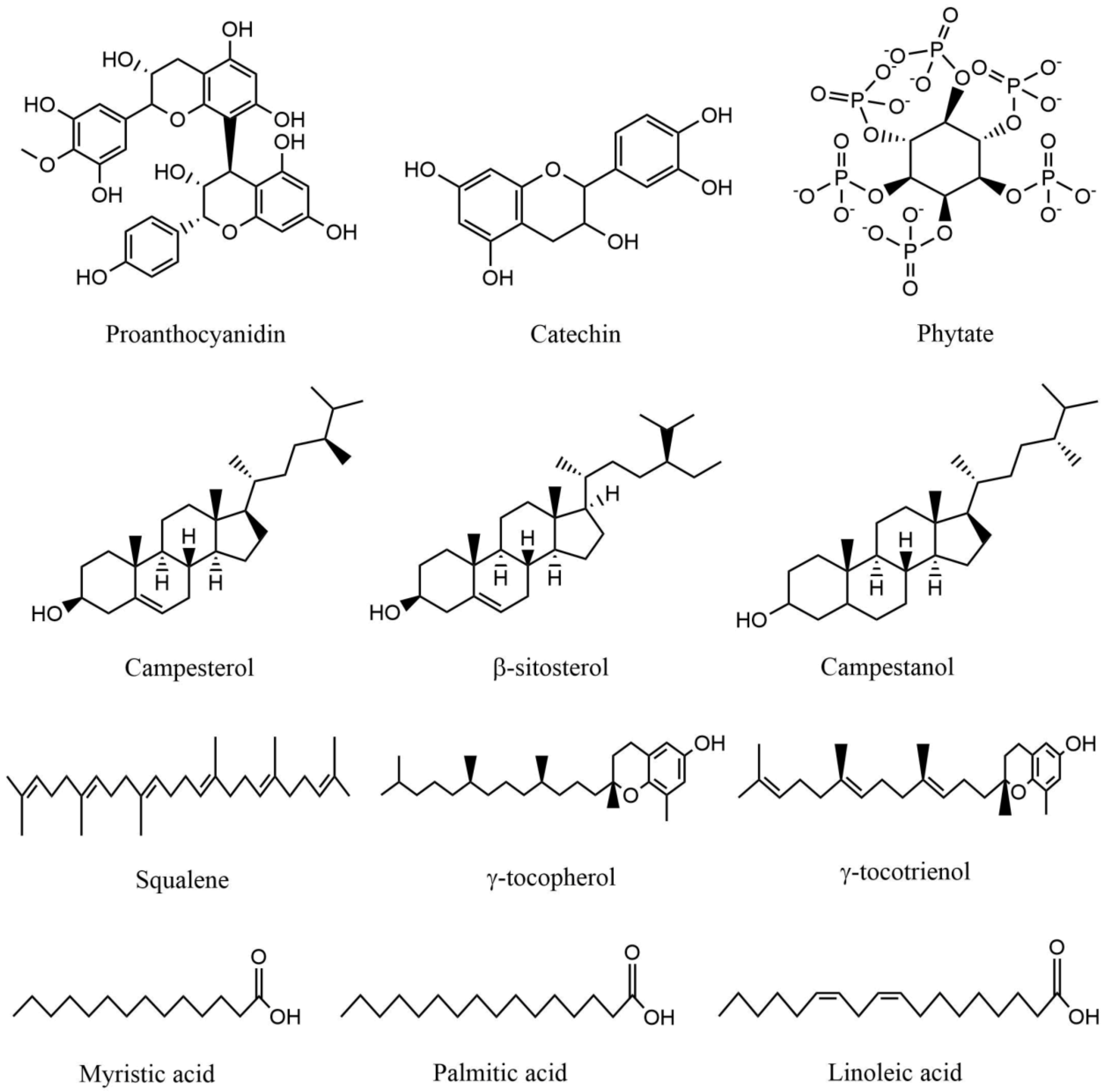

Figure 1. Structure of chemical compounds from Macadamia genus.

The DPPH radical scavenging activity of the macadamia oil was 0.17 mM TAEC/kg, and the ratio of Lipophilic Fractions (LF)/Hydrophilic Fractions (HF) was 1.31 mM TEAC/kg [39]. Meanwhile, the total lipid-soluble antioxidant capacity of the *M. integrifolia* kernel oils from seven cultivars in Hawaii measured by photo-chemiluminescent (PCL) inhibition assay ranged from 42.53 to 65.78 nmol TE/g oil in 2006 and from 37.48 to 46.81 nmol TE/g oil in 2007. Macadamia kernels contained significant amounts of tocotrienol (T3) and squalene, and these phytochemicals may confer antioxidant activity [19]. The antioxidant activity of macadamia nut peptide with different molecular weights was evaluated by the DPPH method, and the result showed DPPH free radical scavenging activity 80.97%. By increasing the concentration of the protein-peptide component, its antioxidant activity also increased [40].

3.2.2. Antimicrobial activity.

M. integrifolia seeds, leaves, and flowers have been investigated for their antimicrobial activity in some researches. *M. integrifolia* seeds containing the antimicrobial peptide named MiAMP1 (β-barrelins). The MiAMP1 could protect against various phytopathogenic fungi and Gram-positive bacteria with a concentration range of 0.2 - 2 μM [41].

Five extracts (methanol, water, ethyl acetate, chloroform, and hexane) of *M. integrifolia* leaves and flowers displayed antimicrobial activities in the disc diffusion assay. All flower extracts inhibited the growth of 7 bacteria tested (*A. hydrophilia, C. freundi, E. coli, P. mirabilis, S. marcenscens, S. sonnei,* and *B. cereus*) and all 3 of the fungi tested (*A. niger, C. albicans,* and *S. cerevisiae*). Meanwhile, all leaves extracts inhibited the growth of six bacterial species tested (*A. hydrophilia, C. freundi, E. coli, P. mirabilis, P. fluroscens,* and *S. marcenscens*) and two of the fungi tested (*C. albicans,* and *S. cerevisiae*) [12].

M. integrifolia nuts and leaves that extracted by methanol and water expressed antimicrobial properties against *P. mirabilis*. The minimum inhibitory concentration (MIC) of methanol extracts were 15 µg/ml and 2790 µg/ml for nuts and leaves, respectively. Besides, water extracts had MIC values 558 µg/ml and 4378.2 µg/ml for nuts and leaves, respectively [42]. However, only methanol extract from *M. integrifolia* flowers from Australia was reported to inhibit *A. hydrophilia* using disc diffusion assay [43]. *M. integrifolia* oil also showed inhibitory activity against *Pseudomonas aeruginosa* with MIC > 2.0% v/v [44].

3.2.3. Anti-dyslipidemia activity.

Macadamia nuts intake on 25 mildly hypercholesterolemic subjects for 5 weeks resulted in a significant decrease of total cholesterol (from 5.66 to 4.94 mmol/l), Low-Density Lipoprotein (LDL)-cholesterol (from 3.68 to 3.14 mmol/l), and non- High-Density Lipoprotein (HDL) cholesterol (from 4.41 to 3.83 mmol/l) due to their high- monounsaturated fatty acid MUFA contents, especially palmitoleic and oleic acid [45]. Macadamia nuts consumption also reduced overweight subjects' total cholesterol from 5.38 to 5.1 mmol/l [46]. Mixed nuts, indeed macadamia nuts, showed significant decreases in triglycerides, total cholesterol, and non-HDL cholesterol [47].

Many literature reviews exhibited the effect of macadamia nuts on reducing triglycerides, total cholesterol, and LDL-cholesterol. Macadamia nut consumption on hypercholesterolaemic and overweight subjects could decrease triglycerides in 5-10 weeks [48]. Diet enriched with macadamia nuts on 14 subjects with hypercholesterolemia for 5 weeks also reduced total cholesterol and LDL-cholesterol [49]. Meanwhile, recent well-controlled intervention studies with macadamias showed LDL-cholesterol reductions ranging from 4% to 11% versus comparator diets, confirming macadamia nut's cholesterol-lowering efficacy [50].

MUFA-rich content in macadamia nuts is likely to affect cardiovascular health [51] beneficially. Alasalvar *et al*. (2020) reported that macadamia nut consumption was suggested by Food and Drug Association (FDA) to reduce coronary heart disease (CHD) risk [52].

3.2.4. Anti-inflammatory activity.

Cell culture experiments were performed using murine macrophages (RAW264.7) to study macadamia oily nut extract's capacity to modulate inflammatory processes by chromatographic analysis. The results showed that macadamia oily nut extract significantly reduced the lipopolysaccharide (LPS)-induced expression of iNos, Tnfα, Il1β, and Il6 mRNAs of RAW264.7 macrophages up to 71%, 29%, 57%, and 27%, respectively [53].

Moreover, macadamia nut consumption (equivalent to 15% energy intake) for 4 weeks resulted in a 22.5% reduction of leukotriene B4 LTB_4 (plasma markers of inflammation) concentration in the plasma [37]. Mixed nuts containing macadamia nuts could also reduce hepatic expression of siklooksigenase-2 COX-2, which produces pro-inflammatory prostaglandins from arachidonic acid [47].

3.2.5. Dietary controlled.

The previous research stated that consumption of macadamia oil and high fat showed a decrease in body mass index in rats (5.8 kg/m^2) compared to only high fat consumption (6.2 kg/m^2) [54]. Kim *et al*. (2017) reported that macadamia nuts in a nut-enriched diet on 101 overweight subjects for 18 months could decrease 1.6 kg/m^2 BMI, 6.9 cm waist circumference, and 4.1 kg body weight in the moderate-fat group, while decreased 1.4 kg/m^2 BMI, 2.6 cm waist circumference and 2.9 kg body weight in the low-fat group [49]. Dietary supplement capsules of macadamia oil contained nutritional and health-maintenance properties, such as polyunsaturated fatty acids (2.8-4.7%) and large amounts of monounsaturated fatty acids (80%) [55].

3.2.6. Anti-tyrosinase activity.

El Hawary *et al.* (2020) evaluated the extract's anti-tyrosinase activity, fractions, and isolated compound from macadamia. The results showed extract had tyrosinase inhibitory activity IC_{50} 85 mg/ml and ethyl acetate fraction 60 mg/ml and n-butanol fraction 75 mg/ml. Meanwhile, gallic acid had a strong anti-tyrosinase activity with IC_{50} 56 mg/ml [56].

3.2.7. Chemopreventive activity.

Macadamia nut fermentation produced 19.59 mmol/l of butyrate acid (one of the main short-chain fatty acids), whereas it could inhibit proliferation and induced apoptosis and differentiation in colon cancer cells histone deacetylase inhibitor [57]. The macadamia nuts extract exposed weak antiproliferative activity to inhibit Caco-2 colon cancer cell proliferation with EC_{50} values 86.9 mg/ml [35].

3.2.8. Non-alcoholic fatty liver disease (NAFLD) prevention activity.

Hepatic steatosis belongs to non-alcoholic fatty liver disease (NAFLD) correlated to fructose/sucrose-induced hepatic lipogenesis. Research by Siddiqui *et al*. (2015) demonstrated that macadamia nut oils could inhibit the development of sucrose/fructose-induced hepatic steatosis in C57BL/6 mice due to high-unsaturated fatty acids content [58].

4. Conclusions

The Macadamia genus had various phytochemical compounds and pharmacological activities. Macadamia genus's phytochemical compounds had few pharmacological activities such as antioxidant, anti-inflammatory, anti-dyslipidemia, and antimicrobial. Further research is required to explore the other parts of Macadamia genus plants' potential chemical constituents and pharmacological activities.

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Conflicts of Interest

The authors declare no conflict of interest.

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