wjpmr, 2025, 11(9), 347-351

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH
www.wjpmr.com

SJIF Impact Factor: 6.842

Research Article
ISSN (O): 2455-3301
ISSN (P): 3051-2557

PHENOLIC COMPOUNDS AND ANTIOXIDANT ACTIVITY OF *DIDIEREA MADAGASCARIENSIS* BAILL. (DIDIEREACEAE) LEAVES

Andrianjato Tartin[1,2,3]*, Ralaivaon-dratsitonta Jumael Edith Fabrice[2], Andrianarijaona Mamy[2], Razanakoto Jacquelin Albert[4], Rasolofonirina Hubert Xavier[3], Léa Herilala Rasoanaivo[3] and Randrianasolo Rivoarison[1]

[1]Analytical Chemistry and Formulation Laboratory, Faculty of Sciences, University of Antananarivo.
[2]Geosciences, Physics, Environmental Chemistry and High Pathogenic System Doctoral School (GPCEHP), University of Toliara, Toliara 601 Madagascar.
[3]Laboratory of Natural Substances Chemistry and Biological Organic Chemistry, Faculty of Sciences, University of Antananarivo, B.P. Box 906, Antananarivo 101, Madagascar.
[4]Doctor Lecturer, Ecole Doctorale Nature, Structure de la Matière et Métrologie Nucléaire (NSMMN), Laboratoire de Chimie, University of Antsiranana, Madagascar.

***Corresponding Author: Andrianjato Tartin**
Analytical Chemistry and Formulation Laboratory, Faculty of Sciences, University of Antananarivo.

Article Received on 09/07/2025 **Article Revised on 30/07/2025** **Article Accepted on 20//08/2025**

ABSTRACT

Background: ***Didierea madagascariensis*** Baill. is a plant endemic of Madagascar. Traditionally, a decoction of its leaves is used to relieve back pain and reduce blood pressure. After childbirth, it is used by women as a bath three months after delivery to promote the closure of the cervix, facilitate the discharge of lochia, and cleanse the uterus.[1,2] **Aim of the study:** This work aims to evaluate the chemical constituents and antioxidant activity of this plant. **Materials and methods:** The chemical constituents of the crude ethanolic, hexane, ethyl acetate and butanolic extracts of the leaves were studied. Column chromatography and TLC methods allowed the isolation of products. The structures of the isolated products were identified by concerted analysis of the 1D and 2D NMR spectra and by comparison with the literatures. The hexane, ethyl acetate and butanolic extracts were used for antioxidant activity using DPPH° free radical scavenging. **Results:** According to this method, crude ethanolic extract of *Didierea madagascariensis* leaves exhibited an antioxidant capacity (IC_{50}= 6.56 µg / ml), the antioxidant capacity being more powerful than α-tocopherol (11.43 µg / ml), used as standard drug. Its antioxidant capacity is focalised in ethyl acetate extract (IC_{50}= 5.43 µg/ml). The fractionation of the ethyl acetate and butanolic extracts led to the isolation of four phenolic compounds: 7-hydroxyisoformonetin $^{(P1)}$, quercetin $^{(P2)}$, 1,6-dihydroxy-3,7-dimethoxy-2-(3,8'-dimethyloct-2',7'-dienyl)xanthone $^{(P3)}$ and scutellarin $^{(P4)}$.

KEYWORDS: Phenolic compounds, NMR, Antioxidant, *Didierea madagascariensis*.

1. INTRODUCTION

Didierea is a genus of flowering succulent plants that belongs to Didiereaceae family. It includes two recognized species: *Didierea madagascariensis* Baill. and *Didierea trollii* Capuron & Rauh.[3] Both species are endemic to Madagascar, where they are found in the spiny forest and xerophytic thicket ecosystems of the southern part of the island.[4]

Didierea madagascariensis is a succulent tree or shrub characteristic of these vegetation formations. Locally known as Sogny or Sohongy, this species plays an essential role in traditional medicine and the daily life of communities in southern Madagascar.[5]

To the best of our knowledge, no previous phytochemical and pharmacological investigations have been performed on this species. As a continuation of our study aiming to discover novel chemical structures that can have biological activities from endemic medicinal plants of Madagascar, we carried out a phytochemical investigation of *D. madagascariensis* leaves. The fractionation of the ethyl acetate and butanolic extracts led to the isolation of four phenolic compounds. The structural identification of phenolic compounds from this species are described herein.

2. MATERIALS AND METHODS

2.1 General

TLC were performed on aluminium silica gel 60 F254 (Merck) plates (0.2 mm layer thickness). Spots were visualized using UV lamp (254 and 366 nm) and

spraying with sulfuric acid reagent. Column chromatography was performed on silica gel 60 (6.3-20 µm) (Merck, Darmstadt, Germany). NMR spectra were recorded with a Brüker AV-400 with a cryoprobe for ^{1}H, ^{13}C RMN. Chemical shift values are in δ (ppm) using the peak signals of the solvent $CDCl_3$ as reference, and coupling constants are reported in Hz.

2.2 Plant material

Didierea madagascariensis leaves were collected from the Andatabo forest, Toliara, in southwestern part of Madagascar, on September 16, 2020. Following identification at the Tsimbazaza Zoological and Botanical Park, Antananarivo, a voucher specimen (TAR-001) was deposited at the Laboratory of Analytical Chemistry and Formulation (LCAF), University of Antananarivo, Ampasampito, Madagascar. The leaves were air-dried at room temperature, then ground, and the resulting powder stored until use.

2.3. Extraction

The powdered of *Didierea madagascariensis* leaves (500 g) were extracted with 2000 mL of 90% ethanol at room temperature over 7 days, then filtered. The ethanol was evaporated under reduced pressure to yield 104.56 g of extract. This ethanolic extract was suspended in warm water (40˚C) and subsequently partitioned with hexane, ethyl acetate (AcOEt), and n-butanol (n-BuOH).

2.4 Phytochemical screening

The detection of main classes of phyto-constituents such as polysaccharides, flavonoids, saponins, quinones, triterpenoids, steroids, leucoanthocyanins, tannins, alkaloids, coumarins, and anthocyanosides were conducted on the crude ethanolic extract according to methods previously published. Appearance of specific colors or precipitates indicates the presence of the targeted metabolites.

2.5 Isolation

The ethyl acetate extract (5 g) was chromatographed over a silica gel column (150 g), eluting successively under isocratic conditions of hexane/AcOEt/MeOH (50:40:10) and (50:35:15), to give 160 fractions of 10 ml. Fractions (8→17) were chromatographed by preparative TLC using hexane/AcOEt/MeOH (50:40:10 / V/V/V) as eluent, affording product P1 (7 mg). Fractions (26→67) were purified with LH-20 using DCM/MeOH (1:1,V/V) as eluent to give compound P2 (10 mg). The butanol extract (5 g) was chromatographed on silica gel column (150 g), eluting under isocratic condition of hexane/ AcOEt/MeOH (10:40:50, V/V/V) to give 15 fractions of 50 ml. Fraction C3 was further chromatographed on sephadex LH-20 eluting with MeOH to give a product P3 (8 mg). Compound 4 (7 mg) was obtained after successive chromatographic purification of fraction C4.

2.6 Antioxidant assay

Qualitative test: The qualitative antioxidant was carried out according to the bioautography method. Briefly, the extracts to be tested are deposited in solution on a silica plate. The chromatoplate is sprayed with a solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) in methanol (2 mg/ mL). An active product has a yellow spot on a purple back ground antioxidant test.

Quantitative test: The quantification of the antioxidant product is carried out according to the method of Brand Williams et al (1995) and Sanchez Moreno et al (1998) with some modifications.[6,7,8] The DPPH (25 mg) is dissolved in 100 ml of methanol. This preparation is stored in the dark. Ten milliliters of this solution are added with 45 ml of methanol. Cascade concentrations of the extract to be tested ranging from (2 mg / ml to 0.125 mg / ml) were prepared. In dry tubes, 200 µl of each concentration were respectively mixed with 3800 µl of the 4.5% DPPH solution. Blanks consisting of 3800 µl of the 4.5% DPPH solution and 200 µl of methanol are also prepared. The test is repeated in triplicate and incubated in the dark for 60 min. The same procedure is applied to the control consisting of vitamin E (α-tocopherol). For the reading, the absorbance is measured using a spectrophotometer at the wavelength of 517 nm. The antioxidant activity which expresses the capacity to scavenge the free radical is estimated by the percentage of discoloration (percentage of inhibition) of DPPH in solution in methanol. The percent inhibition is calculated using formula (1).

$$\text{Percent inhibition (\%)} = \frac{[(Ac - As)}{(Ac)]} \times 100$$

Ac = the absorbance of the control
As = the absorbance of the sample.

3. RESULTS

3.1 Extraction

Maceration in EtOH of 500 g of the plant material yielded 104.56 g (20.91%) of crude ethanolic extract. Maceration in solvents in increasing polarity of 500 g of the plant material furnished 13.45 g (2.69%) of hexane, 24.52 g (4.90%) of ethyl acetate, and 21.43 g (4.29%) of butanol extracts.

3.2 Phytochemical screening

The phytochemical screening was performed on the crude ethanolic extract by means of different chemical assays. It revealed the presence of flavonoids, leucoanthocyanins, tannins, steroids, terpenoids, and polysaccharides.

3.4 Identification

The structures of the isolates were determined through analysis of their spectroscopic data. The NMR spectra of all isolated compounds are consistent with polyphenol skeletons. By means of 1-D and 2-D NMR spectra and comparison with literature compounds P1,P2,P3 and P4 are recognized as 7-hydroxyisoformonetin[9], quercetin[10,11], 1,6-dihydroxy-3,7-dimethoxy-2-(3,8'-dimethyloct-2',7'-dienyl)xanthone[12], and scutellarin[13,14] respectively (Figure 1).

7-Hydroxyisoformonetin (P1): Colorless crystals
^{1}H NMR (600 MHz, $CDCl_3$) δH ppm: δH: 7.03 (1H, d, J = 8.0 Hz, H-6'); 6.90 (1H, d, J = 8.0 Hz, H-5); 6.50 (1H, d, J = 2.5 Hz, H-3'); 6.48 (1H, dd, J = 8.0, 2.5 Hz H-5'); 6.35 (1H, d, J = 2.5 Hz, H-8); 6.34 (1H, dd, J = 8.0, 2.5 Hz, H-6); 4.80 (s, 7-OH); 4.32 (1H, ddd, J = 10.0, 3.5, 2.0 Hz, H-2α); 4.02 (1H, dd, J = 10.0 Hz, H-2β); 3.83 (3H, s, OCH_3-2');3.82 (3H, s, OCH_3-4'); 3.57 (1H, m, H-3); 2.99 (1H, dd, J = 15.5, 10.0 Hz, H-4α); 2.89 (1H, m, J = 15.5, 5.0, 2.0 Hz, H-4β). **^{13}C NMR (125 MHz, $CDCl_3$) δC ppm**: 159.9 (C-4'); 158.1 (C-2'); 155.5 (C-7); 155.1 (C-9); 130.6 (C-5); 128.0 (C-6'); 122.5 (C-1'); 115.2 (C-10); 108.1 (C-6); 104.3 (C-5'); 103.4 (C-8); 99.0 (C-3'); 70.2(C-2); 55.6 (OCH_3-4'); 55.5 (OCH_3-2'); 31.7 (C-3); 31.0 (C-4).

Quercetin (P2): Garnet powders
δH (ppm) ^{1}H NMR (600 MHz, $CDCl_3$): 7.69 (1H, d, J = 8.4 Hz, H-2′); 7.56 (1H, dd, J = 8.4, 2.0 Hz, H-6′); 6.90 (1H, d, J = 8.4 Hz, H-5′); 6.59 (1H, d, J = 2.0 Hz, H-8); 6.40 (1H, d, J = 2.5 Hz, H-6). **^{13}C NMR (125 MHz, $CDCl_3$) δC ppm:**176.7 (C-4); 164.4 (C-7); 161.6 (C-9); 157.0 (C-5); 148.4 (C-4′); 147.4 (C-2); 145.5 (C-3′); 136.2 (C-3); 122.5 (C-1′); 120.8 (C-6′); 116.1 (C-5′); 115.6 (C-2′); 103.9 (C-10); 99.0 (C-6); 94.0 (C-8)

1,6-dihydroxy3,7-dimethoxy-2-(3,8'-dimethyloct-2',7'-dienyl) Xanthone (P3): yellow amorphous powder
δ (ppm) ^{1}H NMR (600 MHz, $CDCl_3$):13.10 (1H, s, 1-OH); 7.58 (1H, s, H-8); 6.90 (1H, s, H-5); 6.40 (1H, s, H-4); 6.37 (1H, s, 6-OH); 5.29 (1H, t, J = 6.8 Hz, H-2'); 5.08 (1H, t, J = 6.8 Hz, H-7'); 4.05 (3H,s,7-OMe); 3.95 (3H, s, 3-OMe); 3.39 (2H, d, J = 6.8 Hz, H-1'); 2.05 (2H, m, H-6'); 1.90 (2H, m, H-5'); 1.79 (3H, s, H-4'); 1.60 (3H, s, H-10'); 1.54 (3H, s, H-9'). **^{13}C NMR (125MHz, $CDCl_3$) δC ppm:**178.9(C-9); 163.5(C-3); 159.1 (C-1); 156.2 (C-4a); 152.3(C-6); 152.3 (C-10a); 144.3(C-7); 135.0(C-3′); 131.1 (C-8'); 124.2 (C-7'); 122.0(C-2′); 113.4 (C-8a); 111.5(C-2); 104.6(C-8); 102.3(C-5); 102.1 (C-9a); 89.9(C-4); 56.6 (7-OMe); 55.9 (3-OMe); 39.5(C-5′); 26.4(C-6′); 25.5 (C-10'); 21.0(C-1′); 17.4 (C-9'); 16.0(C-4′).

Scutellarin (P4): pale yellow powder
δ (ppm) ^{1}H NMR (600 MHz, CD_3OD): δH: 7.90 (2H, H-2'/H-6'); 6.85 (2H, H-3'/H-5'); 6.81 (1H, H-8); 6.52 (1H, H-3); 5.28 (1H, H-1"- glucuronide); 4.25 (1H, H-5"); 3.00–4.00 (m, H other Other glucuronides). **δ (ppm) ^{13}C NMR (125 MHz, CD_3OD):** 183.0 (C-4); 171.5 (C-6"); 164.7 (C-2); 162.0 (C-4'); 152.0 (C-7); 149.5 (C-9); 147.3 (C-5); 131.0 (C-6); 129.1 (C-2'/C-6'); 121.7 (C-1'); 116.5 (C-3'/C-5'); 106.5 (C-10); 103.1 (C-3); 101.1 (C-1"- glucuronide); 94.6 (C-8); 76.2 (C-3"); 75.5 (C-5"); 73.4 (C-2"); 72.3 (C-4").

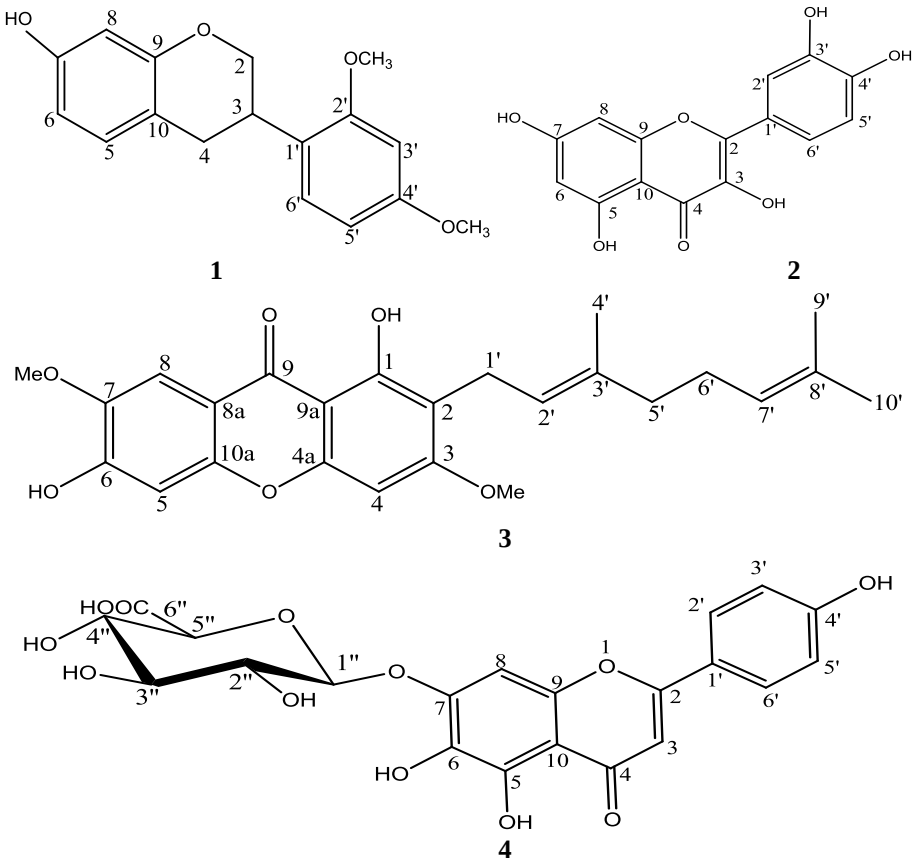
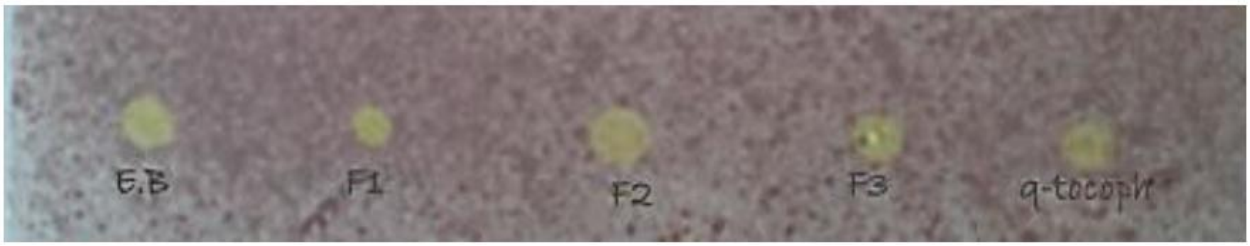


Figure 1: Isolated compounds chemical structures from *Didierea madagascariensis* Baill leaves.

3.5 Free radical scavenging activity on DPPH.

The four extracts crude ethanolic (E.B), hexane (F1), ethyl acetate (F2) and butanol (BuOH) extracts of *Didiereaceae madagascariensis* leaves, contain antioxidant products (Figure 2).



Stationary phase : Silica gel 60
Developer : DPPH/ MeOH (2 mg/ ml)

Figure 2: Qualitative antioxidant test of *Didiereaceae madagascariensis* leaves extracts.

The DPPH is a stable radical with a maximum absorption at 517 nm that can readily undergo scavenging by antioxidant. It has been widely used to test the ability of compounds as free-radical scavengers or hydrogen donors and to evaluate the antioxidant activity of plant extracts and foods.[15]

The scavenging abilities of *Didiereaceae madagascariensis* Baill. leaves extracts were concentration dependent, usually expressed as IC_{50} values, the amount of antioxidant necessary to decrease the initial concentration of DPPH by 50%. Lower IC_{50} value indicates a higher antioxidant activity. The IC_{50} values of each extract are compared with the IC_{50} value of α-tocopherol (Table 1).

Table 1: Inhibition concentration IC_{50} of the sample tested.

Extracts	IP % à 50 µg/mL	IC_{50} (µg/mL)
Crude extract (E.B)	95,43	6,56 ± 0,20
Ethyl acetate (F2)	95,64	5,43 ± 0,15
n-Buthanol (F3)	76,05	33,31 ± 0,10
α- tocophérol	NT	11,43 ± 0,10

In this study, DPPH radical scavenging activity of the tested samples was in the order ethyl acetate > crude ethanolic > α-tocopherol > butanol; the crude ethanolic extract of leaves showed high antioxidant capacity. According to this method, crude ethanolic extract of *Didierea madagascariensis* leaves exhibited an antioxidant capacity (IC_{50}= 6.56 µg / ml), the antioxidant capacity being more powerful than of α-tocopherol (11.43 µg / ml), used as standard drug. Its antioxidant capacity is focalised in ethyl acetate extract (IC_{50}= 5.43 µg/ml).

3. DISCUSSION

The results of this study revealed that the ethanolic extract of *Didiereaceae madagascariensis* Baill. leaves exhibited a significant antioxidant activity. The compounds isolated from ethyl acetate and butanol extracts of the leaves of this species, found in many species, have never been isolated before from Didiereaceae family. Although bioassays were not conducted on these isolated compounds, there were previous studies reporting on their biological activities.[16-18] It has been reported that flavonoids and 1,6-dihydroxy-3,7-dimethoxy-2-(3,8′-dimethyloct-2′,7′-dienyl)xanthone constitute the active biological principles of most medicinal plants with antioxidant and anti-inflammatory properties.[19] Quercetin is also known to be a powerful antioxidant.[20] Scutellarin has been shown to prevent of oxidative damage throught its antioxidant activity.[21] 7-Hydroxyisoformonetin is reported to exhibit both antioxidant and anti-inflammatory properties.[22]

4. CONCLUSION

The results of the present study showed that *Didiereaceae madagascariensis* Baill. leaves has antioxidant activity. This is justify with the isolated phenolic compounds.

REFERENCES

1. **Tabassum, S., et al., et al.** F.Khursheed, A.; Zaman, Q.u.; Bukhari, N.A.; Alfagham, A.; Hatamleh, A.A.; Chen, Y. *Phytochemical Profiling, Antioxidant, Anti-Inflammatory, Thrombolytic, Hemolytic Activity In Vitro and In Silico.*
2. **Randrianarivony, T. N., Randrianasolo, A., Andriamihajarivo, T. H., Ramarosandratana, A. V., Jeannoda, V. H., Rakotoarivony, F., & Bussmann, R. W.** *Useful plants and tradition for pregnancy, child delivery and for postpartum care used by people living around Analavelona forest located in Southwest Madagascar* [Indian Journal of Traditional Knowledge, 2016; 15(1): 68–78.
3. **LLIFLE (Living Interactive Library of Flora and Fauna of Madagascar).** (2025, March 3). *Didierea madagascariensis*. Retrieved March 3, 2025, from https://www.llifle.com/Encyclopedia/SUCCULENTS/Family/Didiereaceae/11208/Didierea_madagascariensis.
4. **Lowry II, P. P., & Schatz, G. E.** The Didiereaceae of Madagascar: a family of succulent plants endemic to the spiny forest." *Cactus and Succulent Journal*, **2002;** *74*(2): 65-74.

5. **Lys Carène Andriamanantsoa.** (n.d.). *Endemic plant of the south of Madagascar: Didierea madagascariensis*. Flora Hotel. Retrieved June 9, 2025, from https://florahotelmada.com
6. **Mohamed E.M.I. Abdou., Olivier R., Louise F. Rakotoarison, Stanislas F. Lahadson, Lovasoa Rakotondramasy., Anne W. and Léa H.Rasoanaivo** ; Chemical study of *Phylloxylon xylophylloides* Baker and assessment of its anti-hyperglycaemic activity in Glucose-loaded Normal Rabbits; *Journal of Pharmacognosy and Phytochemistry*, 2020; 9(2): 2278-2282. http://www.phytojournal.com
7. **Daniela B, Laurian V, Ilioara O, Augustin CM, Grigore D, Daniela H et al.** Polyphenolic Composition, Antioxidant and Antibacterial Activities for Two Romanian Subspecies of *Achillea distans* Waldst. et Kit. ex Willd. *Molecules*, 2013; 18: 8725-8739. DOI: 10.3390/molecules18088725
8. **Linda Zandi, Marco Makungu, Joan J. E. Munissi, Sandra Duffy, Rakesh Puttreddy, Daniel von der Heiden, Kari Rissanen, Vicky M. Avery, Stephen S. Nyandoro, and Máté Erdélyi,** Secoiridoids and Iridoids from *Morinda asteroscepa*, J. Nat. Prod., 2020; 83: 2641−2646. https://dx.doi.org/10.1021/acs.jnatprod.0c00447
9. **Huang**, X., **Mu**, B., **Lin**, W., & **Qiu**, Y. (2012). "7-Hydroxy-2',4'-dimethoxy-isoflavan". Records of Natural Products. https://spectrabase.com/spectrum/5rNev82UeWL (consulté le 19 Mars 2024), 6: 166.
10. **Tavakoli**, S., **Khalighi-Sigaroodi**, F., **Khosravi Dehaghi**, N., **Yaghoobi**, M., **Hajiaghaee**, R., **Gholami**, A., **Ghafarzadegan**, R. Isolation and purification of apigenin, quercetin and apigenin 7-O-glycoside from *Apium graveolens* L., *Petroselinum crispum* (Mill.) Fuss, *Allium cepa* L. *J. Med. Plants*, 2022; *21*(83): 72-86.
11. **Sinha**, D., **Biswas**, J., & **Bishayee**, A. Quercetin, a dietary flavonoid, holds promise for cancer prevention and treatment. In *Cancer Therapy*, 2012; 10: 121-128. Bentham Science Publishers.
12. **Rukachaisirikul**, V., **Kamkaew**, N., **Sukavisit**, D., **Phongpaichit**, S., **Sawangchote**, P., & **Taylor**, W.C. Antibacterial xanthones from the leaves of *Garcinia nigrolineata*. *J. Nat. Prod.*, 2003; *66:* 1531-1535.
13. **Ghosh**, S., & **Ghosh**, D. Isolation, structure elucidation, and quantification of flavonoids from *Scutellaria baicalensis*. *Journal of Agricultural and Food Chemistry*, 2003; *51*(25): 7247-7252.
14. **Marston**, A., & **Hostettmann**, K. The chemistry of *Scutellaria*: Flavonoids, triterpenoids and their biological activity. *Phytochemical Analysis*, 2009; *20*(1): 1-18.
15. **Kandhasamy S, Sun CK.** Free radical scavenging activity from different extracts of leaves of *Bauhinia vahlii* Wight and Arn. *Saudi Journal of Biological Sciences*, 2013; 20: 319–325. https://doi.org/10.1016/j.sjbs.2012.12.005
16. **Molyneux, P.** The use of the stable free radical diphenylpicrylhydrazyl (DPPH) for estimating antioxidant activity. *Songklanakarin Journal of Science and Technology*, **2004;** 26(2): 211–219.
17. **Quideau, S., Deffieux, D., Douat-Casassus, C., & Pouységu, L.** Plant polyphenols: Chemical properties, biological activities, and synthesis. *Angewandte Chemie International Edition*, **2011;** 50(3): 586–621. https://doi.org/10.1002/anie.201000044
18. **Pietta, P. G. (2000).** Flavonoids as antioxidants. *Journal of Natural Products*, 63(7), 1035–1042. https://doi.org/10.1021/np9904509
19. **Xanthones:** Negi, J. S., Singh, P., Joshi, G. P., Rawat, M. S. M., & Bisht, V. K. **Naturally occurring xanthones: chemistry and biology.** *Journal of Applied Chemistry*, 2013; 2013: 1–9. https://doi.org/10.1155/2013/621459
20. **Quercetin**: Boots, A. W., Haenen, G. R., & Bast, A. **Health effects of quercetin: from antioxidant to nutraceutical.** *European Journal of Pharmacology*, 2008; 585(2–3): 325–337. https://doi.org/10.1016/j.ejphar.2008.03.008
21. **Scutellarin :** Zhang, T., Chen, X., Qu, L., Wu, J., Cui, R., & Zhao, Y. **Scutellarin; A review of the pharmacological effects and mechanisms in cardiovascular and cerebrovascular diseases.** *Frontiers in Pharmacology*, 2016; 7: 302. https://doi.org/10.3389/fphar.2016.00302
22. **7-Hydroxyisoformononetin**: Lin, F., Jiang, H., Ding, H., & Zhai, X. **Isoflavones from traditional medicinal plants: Pharmacological activities and potential therapeutic applications.** *Frontiers in Pharmacology*, 2019; 10: 1575. https://doi.org/10.3389/fphar.2019.01575