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Distribution of Naturally Occurring Anthraquinones, Iridoids and Flavonoids from *Morinda* Genus: Chemistry and Biological Activity

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Abstract

The present review covers chemistry and bioactivities of anthraquinones, iridoids, and flavonoids from the *Morinda* genus. The plants of *Morinda* species, belonging to the Rubiaceae family, have been used as traditional folk medicine with anti-bacterial, anti-fungal, anti-tumor, anti-helmin, analgesic, anti-inflammatory, and immune enhancing effects. They are rich sources of anthraquinones and iridoids. The relevant 2-methoxy-1,3,6-trihydroxyanthraquinone is one of the most potent quinone reductase enzyme inducers with no cytotoxicity with normal cells. Damnacanthol-3-*O*-β-D-primeveroside and lucidin-3-*O*-β-D-primeveroside displayed a significant reduction of the blood glucose levels in anti-diabetic tests. Additionally, iridoids, 9-*epi*-6α-methoxy geniposidic acid, scandoside methyl ester, asperulosidic acid, showed a more potent inhibitory effect of melanogenesis than the commercial available depigmented arbutin used in cosmetic industry.

Keywords: Rubiaceae, *Morinda*, anthraquinone, iridoid, flavonoid, biological activity

Introduction

Natural products have continuously served as invaluable resources in terms of searching for structurally novel compounds as leads for the development of drugs having many therapeutic applications. With drug discovery from natural products, it is undeniable that plants are one of the richest sources of natural chemotaxonomy having structural diversity with a broad range of pharmacological activities.

Plants of the genus *Morinda*, classified in the Rubiaceae family, are small evergreen trees or shrubs that consist of about 80 species distributed exclusively in tropical climate zones. An abundance of biologically active and structurally intriguing natural products of *Morinda* species has been widely studied. Almost all parts of these plants including roots, barks, stems, leaves, and fruits, have been used as traditional folk medicine having anti-bacterial, anti-fungal, anti-tumor, anti-helmin, analgesic, anti-inflammatory, and immune enhancing effects [1-6]. The popular product derived from the *Morinda* species, for example, noni fruit juice (*M. citrifolia*) namely Tahitian Noni® has been approved as a botanical dietary supplement and novel food.

Morinda species are well known for the chemical diversities of anthraquinones, iridoids, saccharide fatty acid esters, and lignans. Over 200 compounds have been isolated and identified in the *Morinda* plants. However, chemical composition differs largely depending on the part of the plants. Interestingly, anthraquinones and iridoids with different core frameworks were found as the majority of the genus. The anthraquinones are mainly obtained in the roots of the *Morinda* species, whereas the iridoids are found mainly in the leaves. In addition, flavonoids, coumarins, and triterpenoids were also found in other parts of these plants.

Reviews of *M. citrifolia* including ethnobotany, chemistry, biological activity and safety of the botanical dietary supplement as well as phytochemistry, pharmacology, safety of its fruit have previously been published [7,8].

However, systematic studies of the natural products and their bioactivities from the *Morinda* plants have not yet been reported. The aim of this review is thus to systematically outline the secondary metabolites from *Morinda* species from 1995 to the end of 2011, covering the recent progress on phytochemistry, and biological activity of the naturally occurring anthraquinones, iridoids, and flavonoids.

Anthraquinone from *Morinda* genus

Anthraquinone is a major component of phytochemical constituents obtained mainly from the roots and fruits of the *Morinda* genus. The distinctive chemical structure of anthraquinones is represented as two aromatic rings connected by two carbonyl carbons. The ring system may be substituted with a variety of alkyl, *O*-alkyl, phenolic, or methoxy groups that give a large variety of possible structures. Either *O*-methoxy or hydroxyl groups of all isolated components from the *M. species* are mainly located quite uniquely with respect to substitution at C-1 of the anthraquinone core structure as shown in **Table 1**. Recently, the disaccharide anthraquonones such as lucidin-3-*O*-*β*-D-primeveroside **54**, moridone-6-*O*-*β*-D-primeveroside **55**, 1-hydroxy-2-primeverosyloxymethylqnthraquinone-3-olate **60**, 1-hydroxy-5,6-dimethoxy-2-methyl-7-primeverosyloxyanthraquinone **61**, where the disaccharide is located at C-3, C-6, C-2, C-7, respectively, have been reported as depicted in **Figure 1** [9,10].

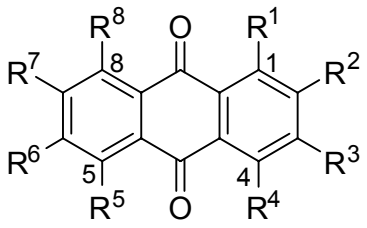


Table 1 Anthraquinones isolated from the *Morinda* genus.

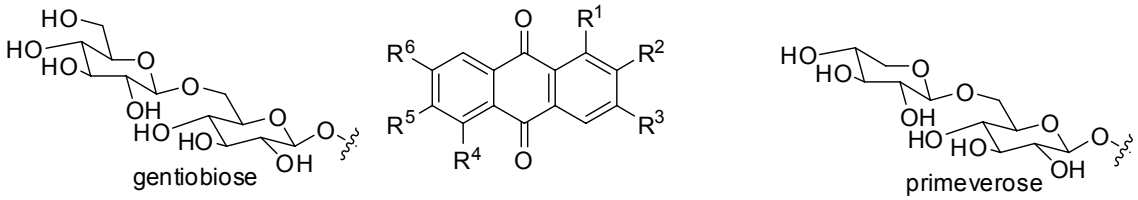
No.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
1	H	CH_3	H	H	H	H	H	H
2	H	COOH	H	H	H	H	H	H
3	H	OCH_3	H	H	H	H	H	H
4	H	CHO	H	H	H	H	H	H
5	OH	OH	H	H	H	H	H	H
6	OCH_3	H	OCH_3	H	H	H	H	H
7	OH	CH_3	H	H	H	H	H	H
8	OH	CH_2OH	H	H	H	H	H	H
9	OH	CHO	H	H	H	H	H	H
10	OH	OCH_2CH_3	H	H	H	H	H	H
11	CH_3	H	OH	H	H	H	H	H
12	OCH_3	OH	H	H	H	H	H	H
13	OCH_3	CH_3	H	H	H	H	H	H
14	OCH_3	H	OH	H	H	H	H	H
15	H	CH3	OH	H	H	H	H	H
16	H	CH_2OH	OH	H	H	H	H	H
17	H	CHO	OH	H	H	H	H	H
18	OH	CH_3	OH	H	H	H	H	H
19	OCH_3	CH_3	OH	H	H	H	H	H
20	OH	CH_2OH	OH	H	H	H	H	H
21	OH	$CH_2OCH_2CH_3$	OH	H	H	H	H	H
22	OCH_3	CH_2OH	OH	H	H	H	H	H
23	OH	CHO	OH	H	H	H	H	H
24	OH	OH	OH	H	H	H	H	H
25	OH	OH	CH_3	H	H	H	H	H
26	OCH_3	CHO	OH	H	H	H	H	H

No.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
27	OH	OCH_3	OH	H	H	H	H	H
28	OH	OCH_3	OCH_3	H	H	H	H	H
29	OH	$CH_2O(CH2)_3CH_3$	OH	H	H	H	H	H
30	OH	CH_2OCH_3	OH	H	H	H	H	H
31	OCH_3	CH_2OCH_3	OH	H	H	H	H	H
32	OCH_3	CH_2OCH_3	OCH_3	H	H	H	H	H
33	OCH_3	OH	OCH_3	H	H	H	H	H
34	OCH_3	OCH_3	OH	H	H	H	H	H
35	OH	CH_3	H	H	H	OH	H	H
36	OH	OH	H	H	H	OH	H	H
37	OCH_3	H	OCH_3	CH_2OH	H	H	H	H
38	OH	OCH_3	OH	H	H	H	H	OH
39	OCH_3	OH	OCH_3	H	H	OH	H	H
40	OH	CH_3	OH	H	H	OH	H	H
41	OH	OCH_3	OH	H	H	OH	H	H
42	OH	OH	H	H	OH	CH_3	H	H
43	OH	H	CH_3	H	H	OCH_3	H	OH
44	OCH_3	CH_3	H	H	OCH_3	OCH_3	H	H
45	OCH_3	OH	H	H	H	H	CH_2OCH_3	OCH_3
46	OH	CH_2OCH_3	H	H	OCH_3	OH	H	H
47	OCH_3	CH_2OCH_3	H	H	OCH_3	OH	H	H
48	OH	CH_3	H	H	OCH_3	OH	H	H
49	OH	CH_3	H	H	OH	OCH_3	H	H
50	OH	CH_2OH	H	H	OCH_3	H	H	OH
51	OH	CH_2OCH_3	H	H	OH	OCH_3	OH	H
52	OH	CH_3	OCH_3	H	H	H	OCH_3	OH

Biological activity of anthraquinone from the *Morinda* genus

The genus *Morinda* is loaded with different types of anthraquinones and its congener. The potential pharmacological activities of the anthraquinones and its derivative have been published. These pertain to antibacterial, anti-cancer, anti-inflammatory, antioxidant, cancer-chemoprevention, anti-microbial activity, and anti-osteoporotic activity. Anthraquinones from the *Morinda* plants and their bioactivities are summarized in **Table 2**.

The effects of anthraquinones on the growth of H1299 human lung cancer cells, HCT116 human colon adenocarcinoma cells, KB human mouth epidermal carcinoma cells, and HeLa human cervical carcinoma cells have been investigated [2,6]. Anthraquinones **4** and **7** showed potent growth-inhibitory effect on HCT116 with IC_{50} values of 5.9 μg/mL and 6.9 μg/mL, respectively. H1299 has been inhibited by anthraquinones **4**, **7**, and **12** with IC_{50} values of 4.9, 4.1, 4.3 μg/mL, respectively. In KB cell lines, anthraquinones **23**, **26**, and **35** have been reported to display moderate growth inhibitory activity with IC_{50} values of 5.99, 6.35, 7.68 μg/mL and showed weak cytotoxicity against HeLa human cervical carcinoma cells. Additionally, anthraquinones **18**, **23**, **26**, and **30** possessed strong activity towards the CEM-SS cell line with CC_{50} of 3, 1.7, 4 and 3 μg/mL, respectively. The anthraquinones **26** and **30** also showed strong cytotoxicity towards MCF-7 cell line with the same CC_{50} value of 3 μg/mL. The significant cytotoxicity against CEM-SS and MCF-7 cell lines was probably due to the combination of the differently substituted types at C-1 to C-3, especially the hydroxylated at C-1 and C-3. Moreover, the presence of the formyl group at C-2 and hydroxylated moiety at C-3 of nordamnacanthal **23** and damnacanthal **26** was found to enhance the anthraquinones microbial activity [11].



	R^1	R^2	R^3	R^4	R^5	R^6
53	OCH_3	CH_2OH	CH_2O-primeverose	H	H	H
54	OH	CH_2OH	CH_2O-primeverose	H	H	H
55	OH	CH_3	H	OH	O-primeverose	H
56	OCH_3	CH_2O-gentiobiose	H	H	H	H
57	OH	CH_2O-primeverose	H	H	H	H
58	OCH_3	CH_2O-primeverose	OH	H	H	H
59	OCH_3	CH_2O-primeverose	O^-	H	H	H
60	OH	CH_2O-primeverose	O^-	H	H	H
61	OH	CH_3	H	OCH_3	OCH_3	O-primeverose

Figure 1 Glycoside anthraquinones isolated from *Morinda* species.

A quinone reductase (QR) bioassay is one of the strategies of cancer chemoprevention for protecting cells from carcinogenesis. This is involved in the catalytic oxidation of NADH or NADPH and consequently deactivates the amount of harmful radicals and electrophiles in phase II metabolizing enzyme [3,5]. With the evaluation of anthraquinones **5**, **12**, **16**, **18**, **27**, **40**, **41**, **48**, and **45**, compounds **5**, **16**, **18**, **40**, **41**, and **50** exhibited QR induction activity with CD values of 12, 0.94, 8.1, 0.56, 0.009, and 1.67 μM, respectively. 2-Methoxy-1,3,6-trihydroxyanthraquinone **41** was found to be potent inducer of QR activity (0.009 μM) which was higher than L-sulforaphane (0.34 μM), a standard inducer, a well-known cancer chemopreventive agent isolated from broccoli [12]. No evidence of cytotoxicity was observed at up to 20 μg/mL (> 69.9 μM). It should be noted that the difference in substitutions pattern at C-1, C-2, C-3 and C-6, especially at C-2 position play an important role in both potency and cytotoxicity in the QR induction assay [3,5].

The tests of three anthraquinones, **53-55**, and two iridoids, **63** and **67,** for hypoglycemic effect have also been investigated. Anthraquinones **53** and **54** displayed a significant reduction of the blood glucose levels at 5 h after administration, but anthraquinone **55** and two iridoids, **63** and **67** have no effects with reducing blood glucose level. Particularly, the anthraquinone having no substituents on one aromatic ring seems to have a significant influence on the hypoglycemic effect [9].

Table 2 Biological activities of naturally occurring anthraquinones from the *Morinda* genus.

Structural name of anthraquinone	*Morinda* specie(s)	Plant part	Biological activity	Ref
Tectoquinone **1**	*M. lucida*	Roots	-	[13]
Anthraquinone-2-carboxylic acid **2**	*M. officinalis*	Roots	-	[14]
2-Methoxyanthraquinone **3**	*M. officinalis*	Roots	-	[15]
2-Formylanthraquinone **4**	*M. citrifolia*	Roots	H1299[a] (IC^e_{50} = 4.9±1.2 μg/mL) HT116[b] (IC_{50} = 5.9±1.5 μg/mL)	[2]
1,2-Dihydroxyanthraquinone **5**	*M. citrifolia*	Fruits	-	[16]
	M. citrifolia	Roots	QR[c] induction assay (CD^d =12.0 μM, IC_{50} = 14.9 μg/mL)	[5]
1,3-Dimethoxyanthraquinone **6**	*M. citrifolia*	Fruits	-	[16]
1-Hydroxy-2-methylanthraquinone **7**	*M. lucida*	Roots	-	[13,14]
	M. citrifolia	Roots	H1299 (IC_{50} = 4.1±1.2 μg/mL) HT116 (IC_{50} = 6.9±1.7 μg/mL)	[2]
	M. citrifolia	Roots	Potential larvucidal of *Aedes aegypti*	[17]
Digiferruginol **8**	*M. officinalis*	Roots	-	[14]
2-Formyl-1-hydroxyanthraquinone **9**	*M. citrifolia*	Roots	-	[2,17]
	M. elliptica	Roots		[18]
2-Ethoxy-1-hydroxyanthraquinone **10**	*M. citrifolia*	Roots	-	[17]
1-Methyl-3-hydroxyanthraquinone **11**	*M. citrifolia*	Roots	-	[2]
Alizarin-1-methyl ether **12**	*M. lucida*	Roots	*C. cucumerinum*[f] (0.5 μg) *C. albicans*[f] (1.0 μg)	[13]
	M. officinalis	Roots	-	[14,15]
	M. citrifolia	Roots	H1299 (IC_{50}=4.3±1.5 μg/mL)	[2]
	M. citrifolia	Fruits	-	[3,19]
	M. elliptica	[g]Cell Cul	Antioxidant [FCT method] (comparable to α-tocopherol)	[4]
1-Methoxy-2-methylanthraquinone **13**	*M. pandurifolia*	Roots	-	[6]
1-Methoxy-3-hydroxyanthraquinone **14**	*M. citrifolia*	Roots	-	[2]
3-Hydroxy-2-methylanthraquinone **15**	*M. officinalis*	Roots	-	[14]
3-Hydroxy-2-hydroxymethyl-anthraquinone **16**	*M. lucida*	Roots	-	[13]
	M. officinalis	Roots	-	[15]
	M. citrifolia	Roots	QR induction assay (CD = 0.94 μM, IC_{50}>20 μg/mL)	[5]
3-Hydroxyanthraquinone-2-carbaldehyde **17**	*M. lucida*	Roots	*C. cucumerinume* (2.0 μg) *C. albicanse* (5.0 μg)	[13]
Rubiadin **18**	*M. officinalis*	Roots	-	[14]
	M. citrifolia	Roots	-	[2]
	M. elliptica	Cell Cul	-	[4]
		Roots		
	M. citrifolia		QR induction assay	[5]
	M. angustifolia	Roots	(CD = 8.1 μM, IC_{50}>20 μg/mL)	
	M. elliptica	Roots	-	[20]
			[h]CEM-SS cells (CC^i_{50} = 1.7μg/mL)	[11]
Rubiadin-1-methyl ether **19**	*M. lucida*	Roots	-	[13]
	M. officinalis	Roots	-	[14,15]
Lucidin **20**	*M. officinalis*	Roots	-	[14]
	M. pandurifolia	Roots	-	[6]
Ibericin **21**	*M. officinalis*	Roots	-	[14]
	M. citrifolia	Roots	-	[2]
	M. angustifolia	Roots	-	[20]
Damnacanthol **22**	*M. lucida*	Roots	-	[13]
	M. angustifolia	Roots	-	[20]

Structural name of anthraquinone	*Morinda* specie(s)	Plant part	Biological activity	Ref
Nordamnacanthal **23**	*M. lucida*	Roots	*C. cucumerinum* (1.0 μg) *C. albicans* (1.0 μg)	[13]
	M. citrifolia	Roots	-	[2,17]
	M. elliptica	Cell Cul	Antioxidant [FCT method] (stronger than α-tocopherol) EBV^{j} activation in Raji cells (IC_{50} = 0.4 μg/mL) inhibition rate 75.0% cell viability 75.8%	[4]
	M. pandurifolia	Roots		
	M. elliptica	Roots	KB^{k} cells (IC_{50} = 5.99 μg/mL) CEM-SS cells (CC_{50} = 1.7 μg/mL)	[6] [11]
Anthragallol **24**	*M. pandurifolia*	Roots	-	[6]
1,2-Dihydroxy-3-methylanthraquinone **25**	*M. officinalis*	Roots	-	[15]
Damnacanthal **26**	*M. lucida*	Roots	-	[13]
	M. citrifolia	Roots	-	[2]
	M. citrifolia	Roots	Potential larvucidal of *Aedes aegypti* KB cells (IC_{50}=6.35 μg/mL)	[17]
	M. pandurifolia	Roots	CEM-SS cells (CC_{50} = 4 μg/mL)	[6]
	M. elliptica	Roots	$MCF\text{-}7^{l}$ cells (CC_{50} = 3 μg/mL)	[11]
	M. elliptica	Roots		[11]
Anthragallol-2-methyl ether **27**	*M. officinalis*	Roots	-	[14]
	M. citrifolia	Fruits	-	[3,19]
	M. citrifolia	Fruits	$EBV\text{-}EA^{m}$ induction (IC_{50}=483 mol ratio/32 pmol TPA)	[21]
Anthragallol-2,3-dimethyl ether **28**	*M. pandurifolia*	Roots	-	[6]
Lucidin-ω-butyl ether **29**	*M. angustifolia*	Roots	-	[20]
Lucidin-ω-methyl ether **30**	*M. elliptica*	Cell Cul	Antioxidant [FCT method] (comparable to α-tocopherol)	[4]
	M. pandurifolia	Roots	-	[6]
	M. elliptica	Roots	CEM-SS cells (CC_{50} = 3 μg/mL)	[11]
	M. elliptica	Roots	MCF-7 cells (CC_{50} = 3 μg/mL)	[11]
3-Hydroxy-1-methoxy-2-methoxymethylanthraquinone **31**	*M. pandurifolia*	Roots	-	[6]
1,3-Dimethoxy-2-methoxymethylanthraquinone **32**	*M. citrifolia*	Roots	-	[2]
Anthragallol-1,3-dimethyl ether **33**	*M. citrifolia*	Fruits	-	[19]
1,2-Dimethoxy-3-hydroxyanthraquinone **34**	*M. officinalis*	Roots	-	[14]
Soranjidiol **35**	*M. elliptica*	Cell Cul	-	[4]
	M. pandurifolia	Roots	KB cells (IC_{50}=7.67 μg/mL)	[6]
Flavopurpurin **36**	*M. pandurifolia*	Roots	-	[6]
Morindicininone **37**	*M. citrifolia*	Stems	-	[22]
1,3,8-Trihydroxy-2-methoxyanthraquinone **38**	*M. officinalis*	Roots	Strong inhibitory effect on osteoclastic bone resorption	[15]
6-Hydroxy-anthragallol-1,3-dimethylether **39**	*M. citrifolia*	Fruits	-	[19]
1,3,6-Trihydroxy-2-methylanthraquinone **40**	*M. citrifolia*	Roots	QR induction assay (CD=0.56 μM, IC_{50}=12.8 μg/mL)	[5]
2-Methoxy-1,3,6-trihydroxyanthraquinone **41**	*M. citrifolia*	Fruits	QR induction assay (CD=0.009 μM, IC_{50}>20 μg/mL)	[3]
Morindone **42**	*M. lucida*	Roots	-	[13]
	M. elliptica	Cell cul	Antioxidant[DPPH assay] (IC_{50}=40.6 μg/mL) Antioxidant [FCT method] (stronger than α-tocopherol)	[4]
Physcion **43**	*M. officinalis*	Roots	-	[14]

Structural name of anthraquinone	*Morinda* specie(s)	Plant part	Biological activity	Ref
			Strong inhibitory effect on osteoclastic bone resorption	[15]
1,5,6-Trimethoxy-2-methylanthraquinone **44**	*M. lucida*	Roots	-	[13]
Morindicinone **45**	*M. citrifolia*	Stems	-	[22]
5,15-di-*O*-methylmorindol **46**	*M. citrifolia*	Fruits	-	[19]
			EBV-EA induction (IC_{50}=475 mol ratio/32 pmol TPA)	[21]
			-	[23]
1,5,15-tri-*O*-methylmorindol **47**	*M. citrifolia*	Fruits	EBV-EA induction (IC_{50} = 386 mol ratio/32 pmol TPA)	[21]
	M. citrifolia	Leaves	-	[24]
Morindone-5-methylether **48**	*M. citrifolia*	Fruits	-	[3,18]
Morindone-6-methylether **49**	*M. citrifolia*	Roots	-	[17]
1,8-Dihydroxy-2-hydroxymethyl-5-methoxyanthraquinone **50**	*M. citrifolia*	Fruits	QR induction assay (CD=1.67 μM, IC_{50}>20 μg/mL)	[3]
1,5,7-Trihydroxy-6-methoxy-2-methoxymethylanthraquinone **51**	*M. citrifolia*	Fruits	-	[23]
1,8-Dihydroxy-2-methyl-3,7-dimethoxyanthraquinone **52**	*M. angustifolia*	Roots	Antimicrobial activities against Zone of inhibition (diameter, mm) *B. subtilis* (14.0 mm, with 13.3μg/disc) *E. coli* (12.5 mm, with 13.3μg/disc) *M. luteus* (13.0 mm, with 13.3μg/disc) *S. lutea* (6.8 mm, with 13.3μg/disc) *C. albicans* (7.5 mm, with 13.3μg/disc) *S. sake* (6.3 mm, with 13.3μg/disc)	[20]
Damnacanthol-3-*O*-*β*-D-primeveroside **53**	*M. citrifolia*	Roots	Reduction of blood glucose level from streptozotocan-induced diabetic mice	[9]
Lucidin-3-*O*-*β*-D-primeveroside **54**	*M. angustifolia*	Roots	-	[20]
	M. citrifolia	Roots	Reduction of blood glucose level from streptozotocan-induced diabetic mice	[9]
Morindone-6-*O*-*β*-D-primeveroside **55**	*M. citrifolia*	Roots	-	[9]
Digiferruginol-1-methylether-11-*O*-*β*-gentiobioside **56**	*M. citrifolia*	Roots	-	[10]
Degiferruginol-11-O-β -primeverside **57**	*M. citrifolia*	Roots	-	[10]
Damnacanthol-11-O-β -primeveroside **58**	*M. citrifolia*	Roots	-	[10]
1-Methoxy-2-primeverosyloxymethyl-anthraquinone-3-olate **59**	*M. citrifolia*	Roots	-	[10]
1-Hydroxy-2-primeverosyloxymethyl-anthraquinone-3-olate **60**	*M. citrifolia*	Roots	-	[10]
1-Hydroxy-5,6-dimethoxy-2-methyl-7-primeverosyloxyanthraquinone **61**	*M. citrifolia*	Roots	-	[10]

[a]Human lung cancer lines (H1299) [b]Human colon adenocarcinoma cell lines (HT116) [c]Quinone Reductase (QR) induction assay [d]Concentration required to double QR activity (CD) [e]Concentration inhibiting cell growth by 50 % (IC_{50}) [f]Bioautography assay [g]Cell cult = Cell Culture [h]T-lymphoblastic leukaemia (CEM-SS cells) [i]50 % cytotoxic concentration (CC_{50}) [j]Epstien Barr Virus activation on Raji cells (EBV activation on Raji cells) [k]Human mouth epiderma carcinoma cell lines (KB) [l]Breast carcinoma (MCF-7 cells) [m]TPA-induced inflammation in mice and on the induction of Epstein-Barr Virus Early Antigen.

Chemistry of iridoid from *Morinda* genus

Iridoid is a monoterpenoid containing cyclopentane ring of iridane skeleton usually fused with a pyran ring. *Morinda* plant leaves were found to be the richest sources of diverse monoterpene iridoids as shown in **Figures 2** and **3**. Based on structural analysis, the majority of these iridoids contains monosaccharides connected to C-1 and either methyl ester or carboxylic acid at C-4. The fused ring junction was observed as *cis*-geometry except for 9-*epi*-6α-methoxy geniposidic acid **64** where there is a *trans*-geometry [25]. The complicated structure based on the stereogenic center of the iridoids **83 - 96** was analyzed mainly as spirolactone molecules as depicted in **Figure 3**, and several of them have been revised by Schripsema *et al.* [26]. In addition, the structural revision of the 6-5 fused ring of moridacin **62** to 5-5 fused ring of borreriagenin **97** was also reviewed [26].

Biological activity of iridoid from *Morinda* genus

The promising potential pharmacological studies of iridoids revealed anti-melanogenesis activity, UVB-induced AP-1 activity, anti-complementary activity, and anti-malarial activity against *Plamodium falciparum*. Iridoids from the *Morinda* plants and their bioactivities are summarized in **Table 3**.

Transcriptional activator protein-1 (AP-1) plays as key role in the development of human skin-cancer by irradiation of UVB. The inhibition of the AP-1 activity has been shown to suppress cell transformation and tumor promotion. Citrifolinin A **80** and citrifolinoside **82** showed significant inhibitory effect with IC_{50} values of 69.6 and 29.0 μM, respectively [35,36].

Interestingly, although iridoids **84 - 87** and **89** had weak cytotoxicity against KB cell line, they showed more potential inhibitory for the proliferation of the malarial parasite (*P. falciparum*). In particular, dehydromethoxy-gaertneroside **89** showed superior inhibition with an IC_{50} 0.04 μM without cytotoxicity [38]. The functionalities of 6"-acetyl, 3'-methoxy and 7'-ketonic carbonyl groups seem to play an important role in enhancing anti-malarial activity independent of cytotoxicity against the host cells. The iridoids **84** and **85** were also observed for anti-complementary activity with IC_{50} values of 58 and 71 μM, respectively.

Iridoids **64**, **65**, **67** showed remarkable inhibition of melanogenesis. These compounds were found to exhibit more potent inhibitory effect of melanogenesis than those of arbutin which is recognized as a useful depigmentation substrate for the skin whitening in the cosmetic industry [25,41].

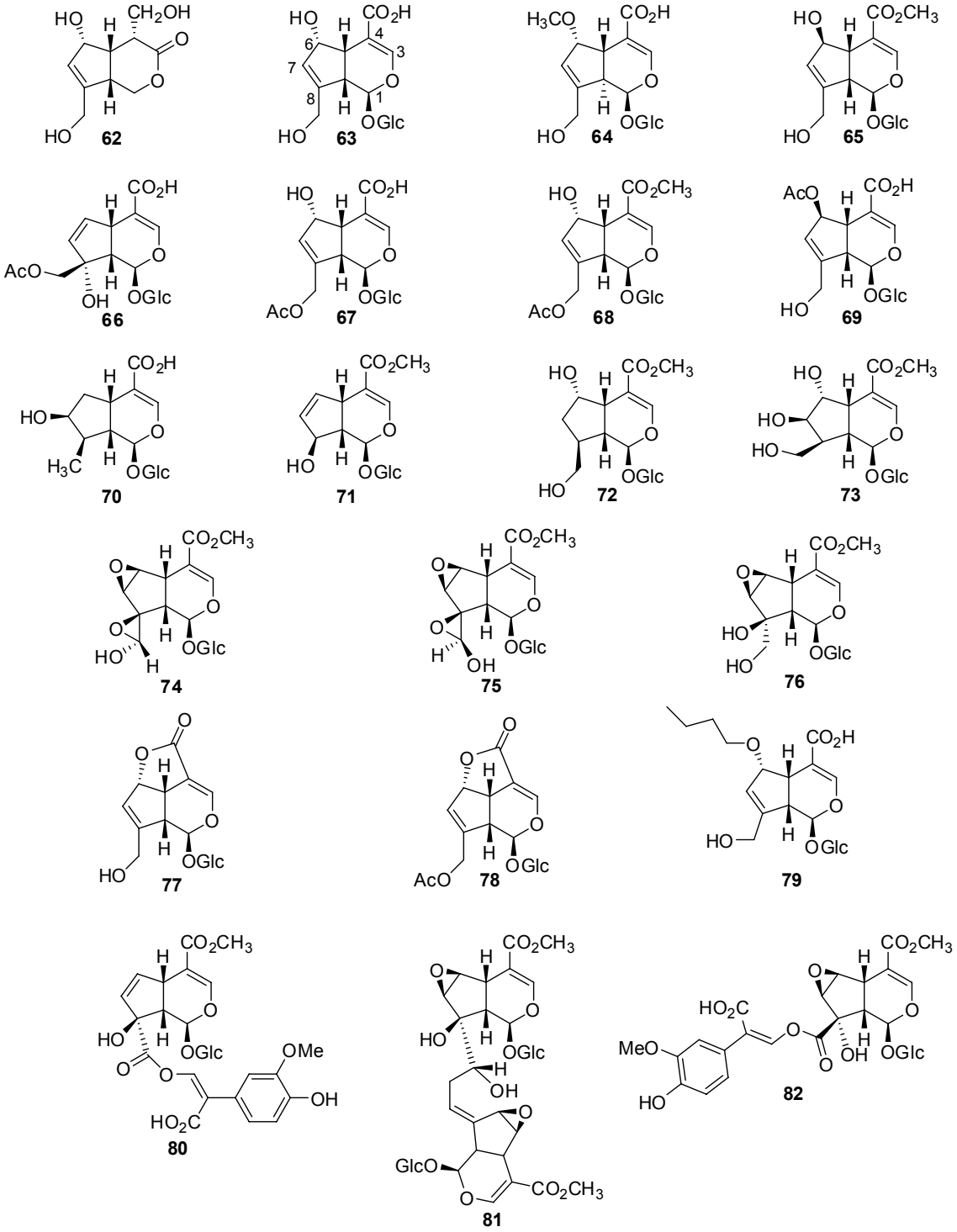


Figure 2 Phytochemical constituents of iridoids isolated from the *Morinda* species.

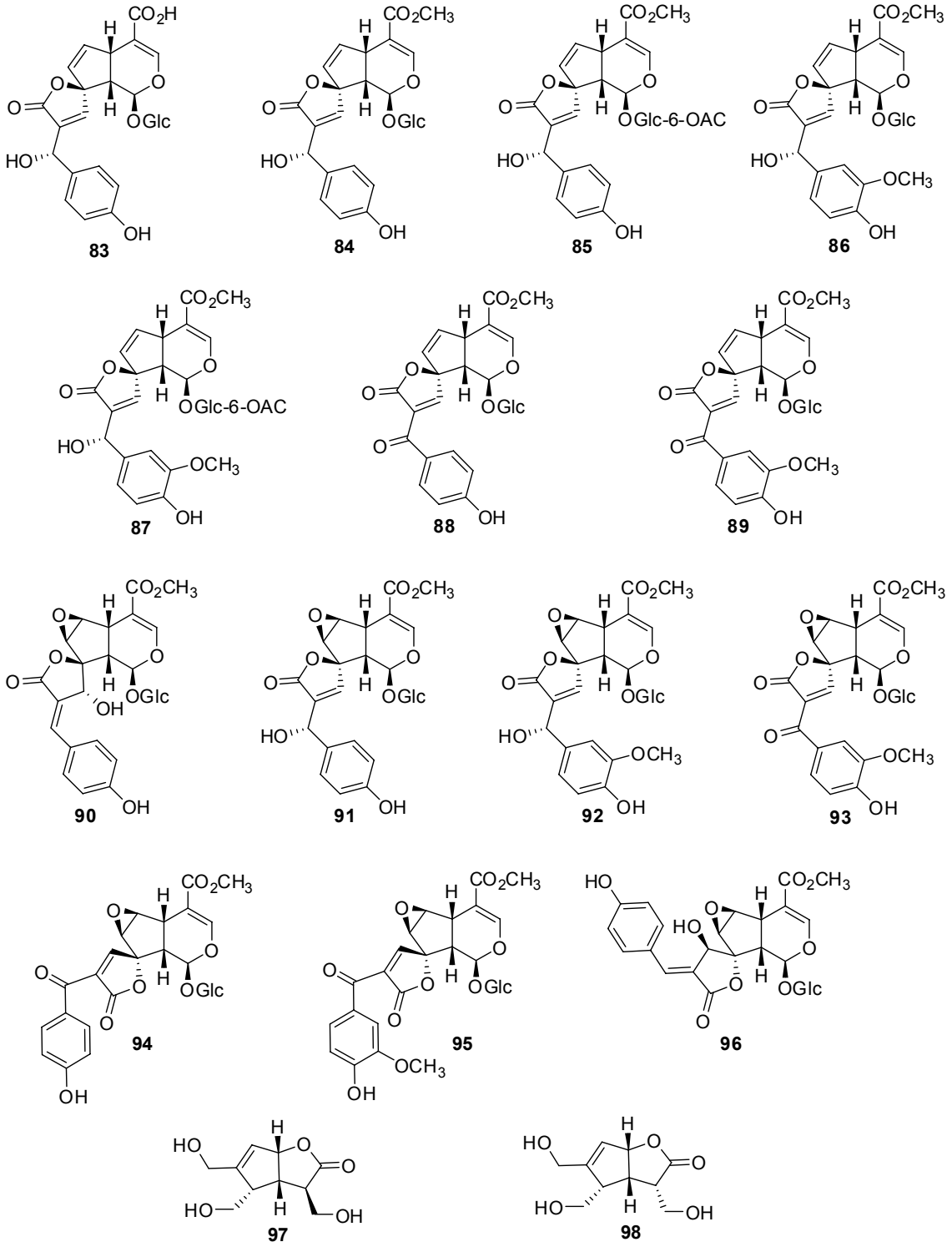


Figure 3 Spirolactone molecules and 5-5 fused ring iridoids isolated from the *Morinda* species.

Table 3 Biological activities of naturally occurring iridoids from *Morinda* genus.

Structural name of iridoid	*Morinda* specie(s)	Plant part	Biological activity	Ref
Morindacin **62**	*M. citrifolia*	Fruits	-	[19]
Deacetylasperulosidic acid **63**	*M. citrifolia*	Fruits	-	[19,25]
	M. citrifolia	Fruits juice	-	[27]
9-*epi*-6α-methoxy geniposidic acid **64**	*M. citrifolia*	Fruits	Antimelanogenesis activity (38 % reduce melanin content at 100 μM)	[25]
Scandoside methyl ester **65**	*M. citrifolia*	Fruits	Antimelanogenesis activity (46 % reduce melanin content at 100 μM)	[25]
10-*O*-Acetylmonotropein **66**	*M. coreia*	Leaves and branches	-	[28]
Asperulosidic acid **67**	*M. citrifolia*	Fruits	EBV-EA induction (IC_{50} = 3485 mol ratio/32 pmol TPA)	[21]
	M. citrifolia	Fruits	Inhibition of tumorigenesis	[29]
	M. citrifolia	Fruits	Antimelanogenesis activity (45 % reduce melanin content at 100 μM)	[25]
	M. elliptica	Leaves, branches	-	[30]
Asperulosidic acid methyl ester **68**	*M. citrifolia*	Fruits, leaves	-	[31]
6-*O*-acetylscandoside **69**	*M. coreia*	Leaves, branches	-	[28]
Loganic acid **70**	*M. citrifolia*	Seeds	-	[32]
Citrifoside **71**	*M. citrifolia*	Leaves	-	[24]
6α-Hydroxyadoxoside **72**	*M. citrifolia*	Fruits	-	[33]
Yopaaoside C **73**	*M. coreia*	Leaves, branches	-	[28]
Citrifolinin Ba **74**	*M. citrifolia*	Leaves	Antioxidant[DPPH assay] (IC_{50}=30 μM, 7.7 %)	[34]
Citrifolinin Bb **75**	*M. citrifolia*	Leaves	Antioxidant[DPPH assay] (IC_{50}=30 μM, 7.7 %)	[34]
6β,7β-epoxy-8-*epi*-splendoside **76**	*M. citrifolia*	Fruits	-	[14]
Deacetylasperuloside **77**	*M. citrifolia*	Fruits, leaves	-	[31]
Asperuloside **78**	*M. elliptica*	Leaves, branches	-	[30]
Rhodolatouside **79**	*M. citrifolia*	Seeds	-	[32]
Citrifolinin **A 80**	*M. citrifolia*	Leaves	UVB-induced AP-1 activity (IC_{50}=69.6 μM)	[35,36]
Citrifolinin **A-1 81**	*M. citrifolia*	Leaves		
Citrifolinoside **82**	*M. citrifolia*	Leaves	UVB-induced AP-1 activity (IC_{50}=29.0 μM)	[36,40]
Gaertneric acid **83**	*M. morindoides*	Leaves	Anticomplementary activity (IC_{50}=69 μM)	[37]
Gaertneroside **84**	*M. morindoides*	Leaves	Anticomplementary activity (IC_{50}=58 μM), Anti-malarial activity (*P. falciparum*) (IC_{50}=0.8 μM)	[37] [38]

Structural name of iridoid	*Morinda* specie(s)	Plant part	Biological activity	Ref
6-Acetylgaertneroside **85**	*M. morindoides*	Leaves	Anticomplementary activity (IC_{50}=71 μM)	[37]
			Anti-malarial activity (*P.falciparum*) (IC_{50}=4.1 μM)	[38]
Methoxygaertneroside **86**	*M. morindoides*	Leaves	Anti-malarial activity (*P.falciparum*) (IC_{50}=21.9 μM)	[38]
6-Acetylmethoxygaertneroside **87**	*M. morindoides*	Leaves	Anti-malarial activity (*P.falciparum*) (IC_{50}=0.1 μM)	[38]
Dehydrogaertneroside **88**	*M. morindoides*	Leaves	-	[37]
Dehydromethoxygaertneroside **89**	*M. morindoides*	Leaves	-	[37]
			Anti-malarial activity (P.falciparum) (IC_{50}=0.04 μM)	[38]
			Revision of structure **80**	[26]
Citrifolinoside A **90**	*M. citrifolia*	Leaves	Revision of structure **96**	[26,39]
Epoxygaertneroside **91**	*M. morindoides*	Leaves	-	[37]
Epoxymethoxygaertneroside **92**	*M. morindoides*	Leaves	-	[37]
Dehydroepoxymethoxy-gaertneroside **93**	-	-	-	[28]
			Revision of structures **82**, **95**	[26]
Morinipticoside **94**	*M. elliptica*	Leaves and branches	-	[30]
Yopaaoside A **95**	*M. coreia*	Leaves and branches	-	[28,30]
Yopaaoside B **96**	*M. elliptica* *M. coreia*	Leaves and branches	-	[28,30]
Borreriagenin **97**	-	-	Revision of structure **62**	[26]
4-epi-Borreriagenin **98**	*M. citrifolia*	Fruit juice	-	[27]

Chemistry and biological activity of flavonoids from the *Morinda* genus

Flavonoids, derived from 2-phenylchromen-4-one, represent a highly diverse class of polyphenolic secondary metabolites which are usually abundant in natural products of higher plant origin, but have been reported as rare case of flavonol glycoside from the *Morinda* species. According to **Figure 4** and **Table 4**, the polar flavonol glycosides **99 - 104** containing flavonoid framework, have been isolated from leaves of *M. citrifolia* and are widely known as natural anti-oxidants in vitro [21,33-34]. Compounds **99 - 101**, **103**, and **104** showed the antioxidant ability to scavenge DPPH at the concentration of 30 μM with 85.8, 4.5, 79.9, 28.6, and 81.3 %, respectively. Compound **102** was found to be inactive in DPPH assay, but it was found to be a potent anti-oxidant activity against both authentic $ONOO^-$ and SIN-1-derivatived $ONOO^-$. Narcissoside **102** having a methoxy group at C-3' was also found to be inactive in DPPH assay whereas quercetin derivatives **99**, **101**, **104** having a hydroxyl group at C-3' displayed a strong anti-oxidant activity [33,34]. Quercetin derivative **101** also exhibited the inhibitory effect on EBA-EA activation induced by TPA compared with those of the known quercetin inhibitor as well as β-carotene. It was found that compound **101** showed comparable activity (578 mol ratio/32pmol TPA) with known quercetin (560 mol ratio/32pmol TPA), but less inhibitory effect than β-carotene (397 mol ratio/32pmol TPA) [21].

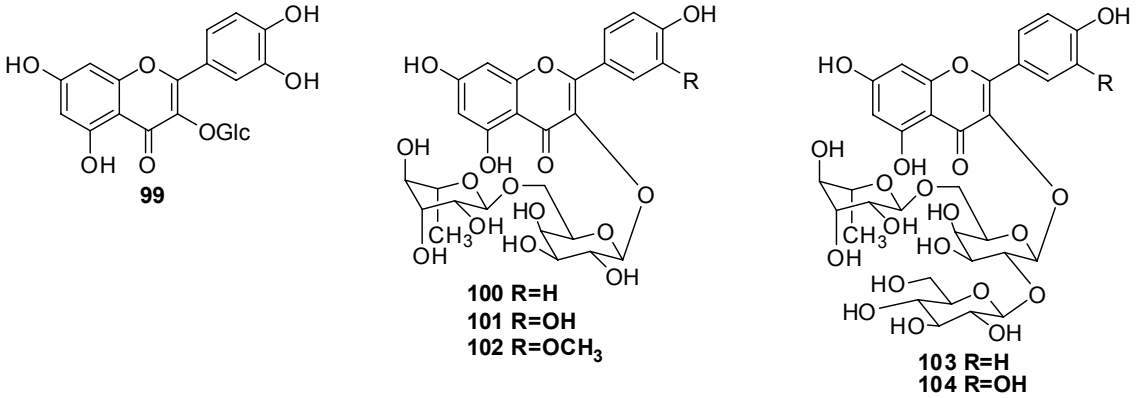


Figure 4 Flavonol glycosides isolated from the *Morinda* species.

Table 4 Biological activities of naturally occurring flavonol glycosides from *Morinda* genus.

Structural name of flavonol glycoside	*Morinda* specie(s)	Plant part	Biological activity	Ref
Quercetin-3-O-β-D-glucopyranoside **99**	*M. citrifolia*	Leaves	Antioxidant[DPPH assay] (IC_{50}=30 μM with 85.8 %)	[34]
Kaempferol-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside **100**	*M. citrifolia*	Leaves	Antioxidant[DPPH assay] (IC_{50}=30 μM with 4.5 %)	[34]
Quercetin-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside **101**	*M. citrifolia*	Fruits	EBV-EA induction (IC_{50}=578 mol ratio/32 pmol TPA)	[21]
	M. citrifolia	Leaves	Antioxidant[DPPH assay] (IC_{50}=30 μM with 79.9 %)	[34]
Narcissoside **102**	*M. citrifolia*	Fruits	Antioxidant [peroxynitrite assay] Authentic $ONOO^-$ (IC_{50}=3.8 μM) SIN-1-derivatived $ONOO^-$ (IC_{50}=9.6 μM)	[33]
Kaempferol-3-O-β-D-glucopyranosyl-(1→ 2)-[α-L-rhamnopyranosyl-(1→ 6)]-β-D-galacopyranoside **103**	*M. citrifolia*	Leaves	Antioxidant[DPPH assay] (IC_{50}=30 μM with 28.6 %)	[34]
Quercetin-3-O-β-D-glucopyranosyl-(1→ 2)-[α-L-rhamnopyranosyl-(1→ 6)]-β-D-galacopyranoside **104**	*M. citrifolia*	Leaves	Antioxidant[DPPH assay] (IC_{50}=30 μM with 81.3 %)	[34]

Conclusion

The phytochemistry of the *Morinda* species has been extensively investigated revealing that they contain anthraquinones, iridoids, flavonoids and other secondary metabolites. These compounds especially anthraquinones, iridoids, flavonoids have been shown to exhibit a wide range of biological activities including anti-oxidant, anti-malarial, anti-tumor, anti-melanogenesis, anti-diabetic, and chemopreventive activities. In addition, the results from quinone reductase (QR) bioassay gave a promising warrant for further research, especially 2-methoxy-1,3,6-trihydroxyanthraquinone **41** which exhibits a higher potent inducer of QR activity (0.009 μM) than the standard L-sulforaphane.

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