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Do Uncommon Plant Phenolic Compounds Have Uncommon Properties? A Mini Review on Novel Flavonoids

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ABSTRACT

Unique plants and their properties, once considered synonymous to medicine, remain a potent source for new compounds in modern science. Plant polyphenols and natural products continue to be investigated for effective treatments for the most persistent of human ailments. In this review, fifty novel plant phenolic compounds have been compiled and briefly described from the previous five years. Select compounds and notable plant species from genus Morinda and Sophora are further expanded on. Traditional medicine plants often contain rich and diverse mixtures of flavonoids, from which rare compounds should receive attention. The bioactivity of crude plant extracts, purified compounds and mixtures can differ greatly, requiring that these interactions and mechanisms of action be investigated in greater detail. Novel applications of uncommon natural products, namely mimosine and juglone, are explored within this review. The 2019 coronavirus pandemic has resulted in abrupt spike of related scientific publications: speculation is made regarding plant natural products and future of antiviral drug discovery.

1. Introduction

Extended processes in land plants have resulted in innumerable phenolic compounds from products of the shikimate pathway, namely aromatic amino acids. Many compounds with unique bioactivity have been derived from phenylalanine, via the phenylpropanoid pathway. Despite being considered “secondary” metabolites, most products from the phenylpropanoid pathway serve an essential role in lignin biosynthesis. Lignin is abundant in plants (20%–30%), crucial in providing structural support of plant cells and has a multitude of industrial applications (Bajwa et al., 2019). The phenylpropanoid pathway in land plants may have originally formed for lignin synthesis as a similar pathway exists in moss (Renault et al., 2017). Non-lignin plant phenolic compounds have less obvious biological functions and have garnered much pharmaceutical attention. A multitude of in vivo functions have been proposed owing to their highly reactive nature, properties which are valued for their effects as antioxidants, chemotherapeutics and as enzyme inhibitors.

Global interest in antiviral compounds, due to the 2019 coronavirus pandemic, has resulted in a tremendous boom in publications. In two years (2018–2020), coronavirus related publications have increased 30-fold, while articles also pertaining to plants increased 5-fold (Fig. 1b). Members of genera *Morus*, *Sophora*, and *Morinda* are of special interest in this review although members of family *Asteraceae*, *Fabaceae*, *Moraceae*, and *Poaceae* are also known to produce a greater diversity of polyphenols (Mottaghipisheh and Iriti, 2020). Research has been steadily growing in these medicinal plants prior to the 2019 coronavirus pandemic (Fig. 1a) and studies which now focus on antiviral properties show promising results. The *Morus* spp. plant extracts and the purified flavone kuwanon G

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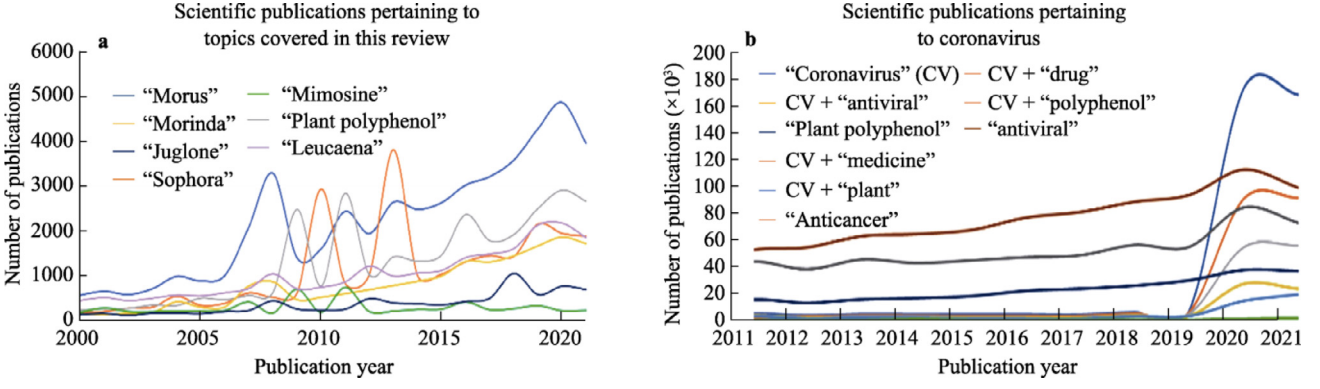

Fig. 1. Yearly publications relating to select search terms was determined by the online application "Dimensions" (https://www.dimensions.ai/). The publication count for year 2021 is an estimation based on results at the time of writing (June, 2021). a: publications relating to plant genera and compounds covered in this review. b: surging interest and publications relating to coronavirus have resulted in increased research of plant natural products.

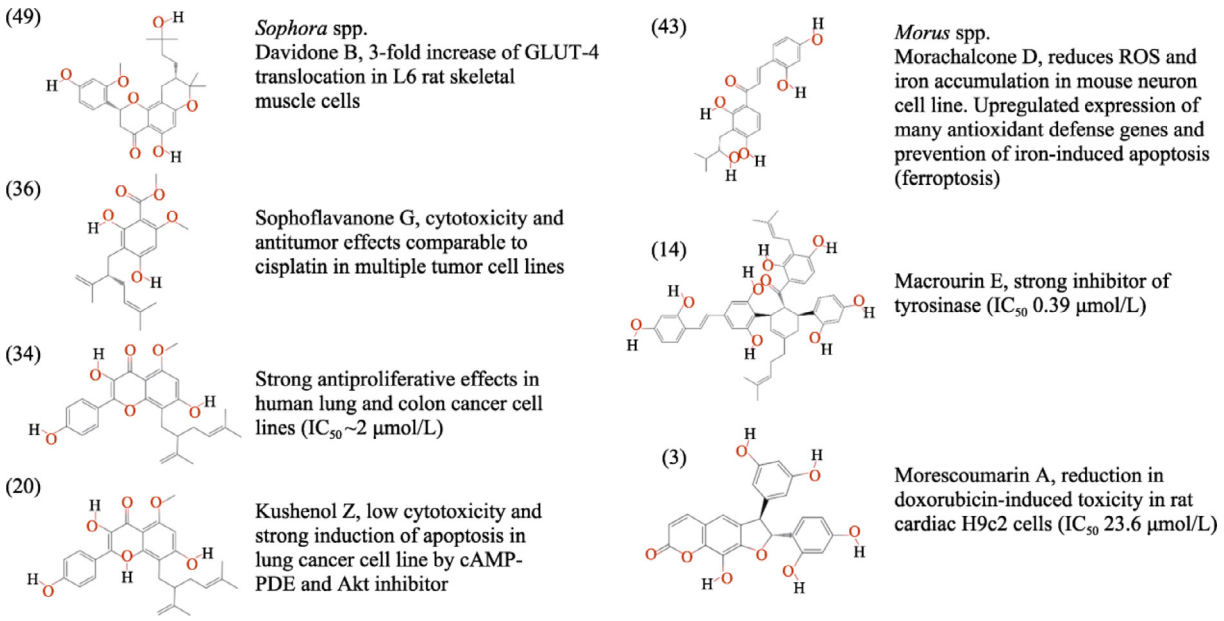

Fig. 2. Select compounds from *Sophora* spp. and *Morus* spp. Table number reference (from Table 1), structure and notable properties are included. Name omitted for (34) as no common name is available.

showed little cytotoxicity and reduced coronavirus-cytopathogenic effects by 60% in cultured human alveolar cells L-132 (Thabti et al., 2020). Plant polyphenol compounds are often investigated for anti-inflammatory, antibacterial and antitumor/anticancer effects, as has kuwanon G for the past thirty years. Antiviral properties are studied to a far lesser extent; recent notable examples from *Faramea bahiensis* (Rubiaceae) leaves with anti-dengue properties (Nascimento et al., 2017), the *Prunus domestica* (Plum) flavonoid rutin preventing Hepatitis C virus cell entry (Bose et al., 2017) and *Cistus incanus* polyphenol-enriched extract against human immunodeficiency virus (HIV) (Rebensburg et al., 2016).

Post-pandemic research is likely to reconsider coronavirus and reinvestigate known flavonoids for antiviral properties. Determining antiviral mechanisms of action and structure-activity relationships precludes the development of synthetic derivatives with improved effects. The semi-synthetic derivative from *Houttuynia cordata* houttuynoid B exhibits 16-fold greater efficiency at inhibiting early stages of Zika virus infection, owing to an unclear mechanism that interferes with virus-to-host membrane fusion (Basic et al., 2019). Antibacterial and antiviral properties of many myricetin derivatives were observed higher than the parent compound; up to ten-fold increase in antibacterial properties and 50% greater inactivation of tobacco mosaic virus (Chen et al., 2019). General rules aim to explain enhanced bioactivity, such as higher lipophilicity of the compound results in greater membrane permeability and hence effect. More specific rules address certain functional groups of flavonoids which have direct effects on enzyme inhibition. Molecules which demonstrate exceptions to the rule or unusual activity are most interesting, thus the objective of this mini review to is to highlight the properties of novel compounds and notable plant species that produce them.

2. Flavonoid production in *Sophora* spp. and *Morus* spp

Many unique polyphenolic compounds are produced by *Sophora* spp., such as pterocarpan flavonoids trifolirhizin, kushenin, sophoraflavanone G and the newly discovered sophoflavanone G (Long et al., 2020) (Fig. 2). At least nineteen novel flavonoids from *Sophora* spp. and twenty-eight from *Morus* spp. were identified in the previous five years of writing this review (Table 1). The diversity of flavonoids from a single source allows for quick analysis of many similar compounds.

Abdel Bar et al. (2020) prepared methylated derivatives of *Morus nigra* L. flavonoids with enhanced toxicity in human breast cancer cell lines, in one instance reducing IC_{50} value eighteen-fold. Many novel prenylated flavonoids in *Morus macroura* exhibit strong inhibitory activity, IC_{50} values < 4 μmol/L, against tyrosine kinase and α-glucosidase (Wang et al., 2018a; 2018b). Similarly, prenylated flavonoids from *Sophora* spp. inhibit glucosidase activities, activate AMP-activated protein kinase, and improve the translocation of glucose transporter 4 (Kim et al., 2017; Ma et al., 2021). Such effects reduce blood glucose concentrations and may treat type II diabetes. Cholesterol and lipid metabolism are affected as well by plant flavonoids. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a newer classification of drugs which increase cell uptake of low-density-lipoprotein cholesterol and are used to treat hypercholesterolemia. The pterocarpan Erybraedin D (*S. tonkinensis*) inhibited PCSK9 protein synthesis with effects resembling berberine, the positive control (Ahn et al., 2019).

Table 1
Collection of fifty articles from the past five years (2017–2021) which have identified a novel polyphenol compound.

No.	Chemical class	Compound	Organism (tissue)	Property/application/activity	Reference
1	Flavanol	Curviflorin	*Plicosepalu scurviflorus* Benth. (shoots)	Identification/purification methods	Al Musayeib et al., 2017
2	Acylated flavonol tetraglycoside	Camellikaempferoside C	*Camellia sinensis* L.O. Kuntze (Leaves)	Inhibition of lipid accumulation in adipose cells	Bai et al., 2017
3	Furocoumarin, flavanone	Morescoumarin A morflavanone A	*Morus alba* L. (root bark)	Cardioprotective effects against doxorubicin induced cell death	Cao et al., 2018
4	Naphthalene glucoside, stilbene glucoside	Rheumone B & piceatannol-4′-O-β-D-(6″-O-acetyl)-glucoside	*Rheum nobile* (rhizome)	Moderate antioxidant activity	Fei et al., 2017
5	Prenylflavonoid	Morusalbols A and B	*Morus alba* (leaves)	Isolation and structure determination	Gao et al., 2018
6	Anthraquinone, napthoquinone	1,2,6-trihydroxy-5-methoxy-9,10-anthraquinone (2R)-6-hydroxy-7-methoxy-dehydroiso-α-lapachone	*Spermacoce latifolia* (whole plant)	Antibacterial activity toward *Bacillus* spp. and in vitro α-glucosidase inhibitory activity	Luo et al., 2017
7	Stilbene glycosides	(9R)-moracin P 3′-O-α-l-arabinopyranoside (9R)-moracin P 9-O-β-d-glucopyranoside (9R)-moracin P 3′-O-β-d-glucopyranoside (9R)-moracin O 10-O-β-d-glucopyranoside	*Morus alba* L. (root bark)	Potential applications as neuroprotective agent, results did not determine activity	Wang et al., 2017
8	Gossypetin glycosides	Gossypetin-3-O-α-L-arabinofuranoside Gossypetin-3-O-α-rhamnopyranoside Gossypetin-3-O-β-xylopyranoside	*Feijoa sellowiana* (fruits, flower buds, leaves)	Antitumor assays and tyrosinase assays performed but analysis of novel compounds unavailable	Aoyama et al., 2018
9	Anthocyanin	Catechin-(4,8)-pelargonidin 3,5 diglucoside afzelechin-(4,8)-pelargonidin 3,5 9 diglucoside	*Zea mays* (pericarp)	Identification/detection methods	Chatham et al., 2018
10	Flavonostilbene	Cajanusflavanols A, B, C	*Cajanus cajan* (leaves)	Anti-inflammatory properties, strong inhibition of nitric oxide production	He et al., 2018
11	Flavonoid glycoside	7-methoxy kaempferol-3-O-α-l-arabinosyl-(1 → 6)-β-d-galactopyranoside kaempferol-3-O-α-l-rhamnopyranosyl-7-O-α-l-rhamnopyranosyl-(1 → 6)-β-d-galactopyranoside	*Astragalus turkestanus, A. xanthomeloides* (aerial parts)	Potential antihyperglycemic drugs, insignificant cytotoxicity and significant inhibition of glucosidase	Janibekov et al., 2018
12	Flavone	5,7-dihydroxy-3,6-dimethoxyflavone 5,7,4′-trihydroxy-3′,5′-dimethoxyflavone 5,7,4′-trihydroxy-3′-methoxyflavone	*Viola odorata* L. (whole plant)	Antidepressant effect in mice	Karim et al., 2018
13	Flavanol	(-)-epiafzelechin-(4α→8)-(-)-catechin (-)-epiafzelechin-(4α→8)-(-)-epicatechin	*Celtis tetrandra* Roxb. (bark)	Cytotoxicity assays, anticancer properties	Seephonkai et al., 2018
14	Prenylated phenolic	Macrourins E, F, G, H	*Morus macroura* Miq. (stems)	Very strong tyrosinase inhibition exhibited by macrourin E	Wang et al., 2018a
15	Phenolic	Macrourins I, J	*Morus macroura* Miq. (stems)	Highly potent in vitro inhibition of α-glucosidase	Wang et al., 2018b
16	Flavanol, flavanone	Nigrenon A, B, C, D, E	*Morus nigra* (twigs)	PPARγ agonistic activity by nigragenon B, potential drug to increase insulin sensitivity	Xu et al., 2018
17	Flavan, stilbene	7,3′-dihydroxy-8,4′-dimethoxyflavan 7,4′-dihydroxy-5,3′-dimethoxy-8-methylflavan 7,4′-dihydroxy-5,3′-dimethoxy-8-prenylflavan 4-hydroxy-5′-methoxy-6″,6″-dimethylpyran-[2″,3″:3′,2′]stilbene 4′-hydroxy-3,5-dimethoxy-2-prenylstilbene	*Cyperus conglomeratus* Rottb. (aerial parts)	Moderate activity towards μ-opioid receptor	Zaki et al., 2018
18	Prenylated flavanones	Sophoratonin A, B, C, D, E, F, G, H (total 8)	*Sophora tonkinensis* (root)	Effect on cholesterol metabolism in HepG2 human liver cells and anti-inflammatory properties	Ahn et al., 2019

(*continued on next page*)

Table 1 (*continued*)

No.	Chemical class	Compound	Organism (tissue)	Property/application/activity	Reference
19	Prenylated flavonostilbene	Alopecurone P	*Sophora pachycarpa* (root)	Insulin resistance in C2C12 myotubes and strong inhibition of tyrosine phosphatase 1B	Boozari et al., 2019
20	Flavonoid	Kushenol Z	*Sophora flavescens* (root)	Antiproliferative activity in lung cancer cells by inhibition of phosphodiesterase and protein kinase B	Chen et al., 2019
21	Anthraquinone	Morindaquinone	*Morinda coreia* (roots)	Extraction and isolation of compound	Chokchaisiri et al., 2019
No.	Chemical class	Compound	Organism (tissue)	Property/application/activity	Reference
22	Prenylated stilbene, flavonoid	Cajanusins A, B, C & cajanusin D	*Cajanus cajan* (leaves)	In vitro cytotoxicity assay against humerous human cancer cell lines	Wu et al., 2019
23	Pyranoflavanone	4′-methoxydereticulatin 2‴-hydroxy,3‴-ethoxylupinifolin	*Derris reticulata* (stem/wood)	High antibacterial activity against various species. Moderate/low activity as antioxidant and glucosidase inhibitor	Issarachot et al., 2019
24	Anthraquinone	2-acetyl-1-hydroxyanthraquinone	*Morinda lucida* Benth. (stem bark)	Extraction and isolation of compound	Kouamé et al., 2019
25	Isoflavone	Ficucaricone A, B, C, D (total four)	*Ficus carica* (fruit)	Anti-inflammatory and antiproliferative	Liu et al., 2019
26	Isoflavane	(3S)-7-hydroxy-8,2′,4′-trimethoxyisoflavane (3S)-7-hydroxy-8,2′-dimethoxy-4′,5′-methylenedioxyisoflavane	*Spatholobus suberectus* Dunn. (stem)	Cytotoxic effects on breast cancer cell line	Peng et al., 2019
27	Flavonoid	Dalpulanone 2-hydroxyisomucronustyrene	*Dalbergia stipulacea* (stems)	Moderate antifungal activity against *Pythium insidiosum*	Posri et al., 2019
28	Coumarin	Meliquercifolin A meliquercifolin B	*Melicope quercifolia* (leaves)	Cytotoxicity assays, anticancer properties	Saputri et al., 2021
29	Prenylated flavonoids	Macarindicin I, II, III, IV	*Macaranga indica* (leaves)	Moderate cytotoxicity by macarindicin II in four human cancer cell lines	Vu et al., 2021
30	Isoflavane	Dolichochaetein A dolichochaetein B	*Astragalus dolichochaete* (roots)	Significant cytotoxicity by dolichochaetein B in three cancer cell lines	Wang et al., 2021
31	Coumarin	Moriramulosid A moriramulosid B	*Morus alba* L. (young twigs)	Potential applications as antihyperuricemic	Yao et al., 2019
32	Stilbene	2′,3,4′-trimethoxy-5-hydroxy-trans-stilbene	*Morus nigra* L. (stem bark)	Cytotoxicity evaluated in carcinoma and breast cell cancer line	Abdel Bar et al., 2020
33	Anthraquinone	(2S, 3R)-1,2,3,4-tetrahydro-2,3,6-trihydroxy-2-methylanthracene-9,10-dione 3,6-dihydroxy-1,2-dimethoxyanthraquinone 1,6-dihydroxy-2-hydroxymethyl-5-methoxyanthraquinone	*Morinda lucida* Benth. (stem bark)	Antibacterial and antifungal properties of novel tetrahydroanthraquinone and crude extract investigated	Longue Ekon et al., 2020
34	Flavanol	4H-1-benzopyran-4-one,2-(4-hydroxyphenyl)-3,7-dihydroxy-5-methoxy-8-[5-methyl-2-(1-methylethenyl)-4-hexenyl]	*Sophora flavescens* (root)	Strong inhibition of lung and colon cancer cell proliferation and induction of apoptosis	Huang et al., 2020
35	Flavone	Astrernestin	*Astragalus ernestii* (root)	Extraction and isolation of compound	Li et al., 2020
36	Flavanone	Sophoflavanone G sophoflavanone H	*Sophora flavescens* Ait. (root)	Cytotoxicity assay, potential antitumor drug	Long et al., 2020
37	Prenylated flavonoid, geranylated stilbene	4′-methyl-8-prenyltaxifolin 6,8-diprenyl-4′-methyl-naringenin 4′-deprenyl-4-methoxymappain	*Macaranga balansae* (fruit)	Cytotoxicity assays on numerous cancer cell lines	Mai et al., 2020

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Table 1 (*continued*)

No.	Chemical class	Compound	Organism (tissue)	Property/application/activity	Reference
38	Anthraquinone	1,6-dihydroxy-2-hydroxymethyl-5-methoxy-9,10-anthracenedione	*Morinda lucida* Benth. (stem bark)	Bactericidal effects against five *Salmonella* strains	Mfonku et al., 2021
39	Stilbene	Caragasinins D caragasinins E	*Caragana sinica* (roots)	Strong inhibition of neuramidase from *Clostridium perfringens*	Park et al., 2020
40	Stilbene dimer	(+)-8b-epi-ampelopsin A	*Chromolaena odorata* L. (aerial parts)	Inhibition of PCSK9 choleresterol metabolism in liver cells	Pel et al., 2020
41	Flavanone	5,3′,5′-trihydroxy-6,7,4′-trimethoxyflavanone 5-hydroxy-6,7,3′,4′,5′-pentamethoxyflavanone	*Gardenia sessiliflora (*leaves and twigs)	Cytotoxicity assays and antiHIV-1 reverse transcriptase assay	Thanasansurapong et al., 2020
42	Coumarin, flavonoid glycoside	3-arylcoumarin liquiritcoumarin crotoliquiritin	*Glycyrrhiza uralensis* (rhizome)	Antioxidant activity by activation of Nrf2 pathway	Wang et al., 2020
43	Prenylated flavonoid	Morachalcone D morachalcone E	*Morus alba* L. (young twigs)	Morachalcone D exhibits protective effects, strong antioxidant activity	Wen et al., 2020
44	Benzofuranone, flavanol	Nigranol A, B	*Morus nigra* Linn. (stem)	α-glucosidase inhibitory activities exhibited by nigranol B	Xu et al., 2020a
No.	Chemical class	Compound	Organism (tissue)	Property/application/activity	Reference
45	Phenolic, pyridine	(2S,2″S)-2,3,8,9-tetrahydro-5-hydroxy-8-(1-methylethenyl)-2-(4-hydroxyphenyl)-4H-furo[2,3-h]-1-benzopyran-4-one-(1″R,2″R)-4-(2-formyl-1H-pyrrol-1-yl)-1-(2-hydroxy-1-methylpropoxy)-butanate (4′S,5′R)-1-[(Tetrahydro-4-hydroxyl-5-oxo-2-furanyl)methyl]-2,4(1H,3H)-pyrimidinedione	*Morus alba* L. (fruit)	Cytotoxicity, antioxidant, and α-glucosidase inhibition assays. Low/moderate activity of new compounds.	Xu et al., 2020b
46	Stilbene	Reflexanbene A, B, C	*Lindera reflexa* Hemsl. (root)	Moderate cytotoxicty in treated human gastric and liver cancer cell lines	Fu et al., 2021
47	Anthraquinone	(±)-Mornaphthoate g, (±)-Mornaphthoate H, 2,8-Dihydroxy-1-methoxyanthracene-9,10-dione, 3,8-Dihydroxyl-1,2-dimethoxyanthracene-9,10-dione, 1,5,8-Trihydroxy-2-methoxyanthracene-9,10-dione, 2-Dimethoxymethylanthracene-9,10-dione (total six)	*Morinda officinalis* (root)	Structural elucidation, antiinflammatory, cytotoxicity and gene expression analysis (qRT-PCR) using murine macrophage cell cultures	Luo et al., 2021a
48	Prenylated isoflavone	(±) Erysectin a	*Erythrina secundiflora* Hassk. (leaves)	Structure determination and moderate cytotoxicity shown in cancer cell lines	Luo et al., 2021b
49	Flavanones, isoflavanone	Davidone A, B, C, D, E & cyclolicoisoflavanone A3 (total six)	*Sophora davidii* (root)	Stimulating GLUT-4 translocation and glucose uptake to treat insulin resitance in type 2 diabetes	Ma et al., 2021
50	Chalcone	2′,4′-dimethoxydihydrochalcone	*Empetrum nigrum* L. (shoots)	Isolation and structure determination	Ponkratova et al., 2021

Notes: The studies listed include entirely novel compounds and not ones discovered for the first time in said species. Considering the diversity of plant polyphenols and considerable number of references, this list is likely incomplete.

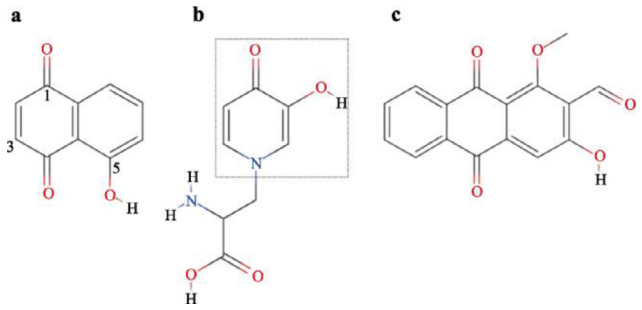

Fig. 3. Juglone (a) with numbered carbons to highlight the C5 hydroxyl group, essential for bioactivity. The amino acid mimosine (b) with 3-hydroxy-4-pyridone side chain enclosed in box. The *Morinda* spp. anthraquinone damnacanthal (c).

3. Novel Anthraquinones in *Morinda* spp

Recently eleven novel compounds have been identified in *Morinda* spp. (Table 1). Damnacanthal (Fig. 3c) is often credited with therapeutic effects, however, crude *Morinda* spp. extracts are likely to contain a diverse collection of anthraquinone compounds. A recent study by Luo et al. (2021a) identified twenty-four anthraquinones isolated from *Morinda officinales* root and demonstrated a range of anti/pro-inflammatory properties of the individual compounds. Damnacanthal analogues require attention to explain the relationship between structure and function of anthraquinones. Different IC_{50} values (Fig. 4) and cytotoxic mechanisms were determined for damnacanthal and nordamnacanthal despite the two compounds differing by a single methyl group (Akhtar et al., 2013; Shaghayegh et al., 2017; Latifah et al., 2021).

Antitumor and anticancer effects of anthraquinones such as damnacanthal stem from the inhibition of various tyrosine kinases which are often overexpressed in cancerous cell lines (García-Vilas et al., 2017). Noni fruit extracts and pure damnacanthal were comparable to the chemotherapeutic drugs paclitaxel and doxorubicin against numerous breast cancer lines (Aziz et al., 2016; Sharma et al., 2016). Damnacanthal is studied less for its antimicrobial effects although recently has been shown effective against *Mycobacterium tuberculosis* (Pollo et al., 2021). Various triterpenoids, lignans and flavonoids found in Morinda have been accredited with moderate antibacterial activity (Sunder et al., 2011; de la Cruz-Sánchez et al., 2019; Zhai et al., 2019).

4. Juglone and Other Naphthoquinones

Derivatives of naphthoquinone provide plants with an effective defense against microbial infection and herbivory. Juglone represents the simplest 1, 4-napthoquinone derivative produced naturally in plants. The phytotoxin juglone is a naphthoquinone produced by the black walnut tree (*Juglans nigra*) and exhibits high reactivity with oxygen and reactive oxygen species (ROS). Chobot (2010) demonstrated ROS generation by juglone as being highly iron-dependent with 10-times more hydroxyl radicals generated by juglone-iron chelates. Results have been compiled from related studies (Chobot and Hadacek, 2011; Chobot et al., 2016) comparing ROS generation by juglone to flavonoids (Fig. 5).

Antibacterial activity of juglone has been observed against *Streptococcus pyogenes* (Macé et al., 2017), *Escherichia coli* (Ynag et al., 2018) and increases the effectiveness of antibiotics against resistant strains of *Staphylococcus aureus* (Zmantar et al., 2016; Yap et al., 2021). The C5 hydroxyl group has been noted as essential for antimicrobial activity in plant naphthoquinones and has been a targeted site for modification (Fig. 3a). The derivative 5-butanoyl-juglone exhibits twice the antibacterial and antifungal properties of juglone (Sánchez-Calvo et al., 2016) however in most cases, modification at C5 for either juglone or plumbagin reduces activity. Hydrophobic derivatives permeate cell membranes more efficiently however the bioactivity of juglone is often sacrificed with such modifications (Fiorito et al., 2016; Sánchez-Calvo et al., 2016). A similar iron binding phytotoxin produced by *Centaurea diffusa*, 8-hydroxyquinoline, is capable of free diffusion across cell membranes as a chelation complex (Tharayil et al., 2009).

5. Mimosine: pyridone metabolites in plants

Pyridone compounds are very rarely produced in nature, have toxic properties and are found mainly in pathogenic fungi (Sassa et al., 1987; Evidente et al., 2006; Eley et al., 2007). Few pyridine and pyridone derivatives have been discovered in plants, such as macaradine in *Lepidium meyenii* (Gonzales and Valerio, 2006), 3-hydroxypyridine in *Portulaca oleracea* (Xu et al., 2017) and mimosine. Further investigation of their biosynthesis, degradation and toxic properties is needed, however mimosine has been extensively studied. Mimosine is a toxic aromatic amino acid with strong iron chelating properties produced by plant species of the genus *Mimosa* and *Leucaena*. Few derivatives of the dihydroxypyridine moiety of mimosine (Fig. 3b) have been investigated except possibly by Dang et al. (2013). In that study, numerous synthesized pyridones exhibited greater fungicidal activity than mimosine. Toxicity is attributed to strong metal chelating capabilities thus causing broad enzyme inhibition, notably though in the inhibition of ribonucleotide reductase, dNTP metabolism and DNA replication (Dai et al., 1994). If excess iron is provided to plant cell cultures or used to supplement leucaena based fodder, toxic effects are mostly eliminated (Gilbert et al., 1995; Gupta and Atreja, 1998). The opposite has been observed in bacteria, the inclusion of iron nearly doubles antibacterial properties of mimosine peptides (Lachowicz et al., 2020).

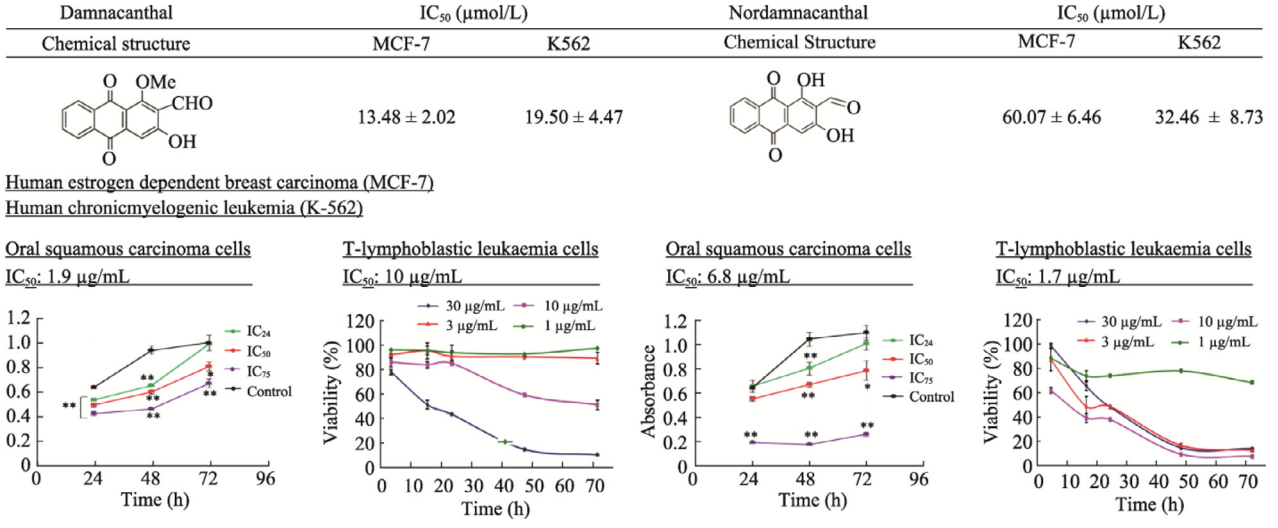

Fig. 4. Comparing toxicity between damnacanthal and nordamnacanthal, two highly similar anthraquinones produced by *Morinda* species. Higher toxicity is observed for damnacanthal, except in T-lymphoblastic cells where even low concentrations have a profound effect on cell viability. Figures taken and modified from Akhtar et al., 2013, Shaghayegh et al., 2017 and Latifah et al., 2021.

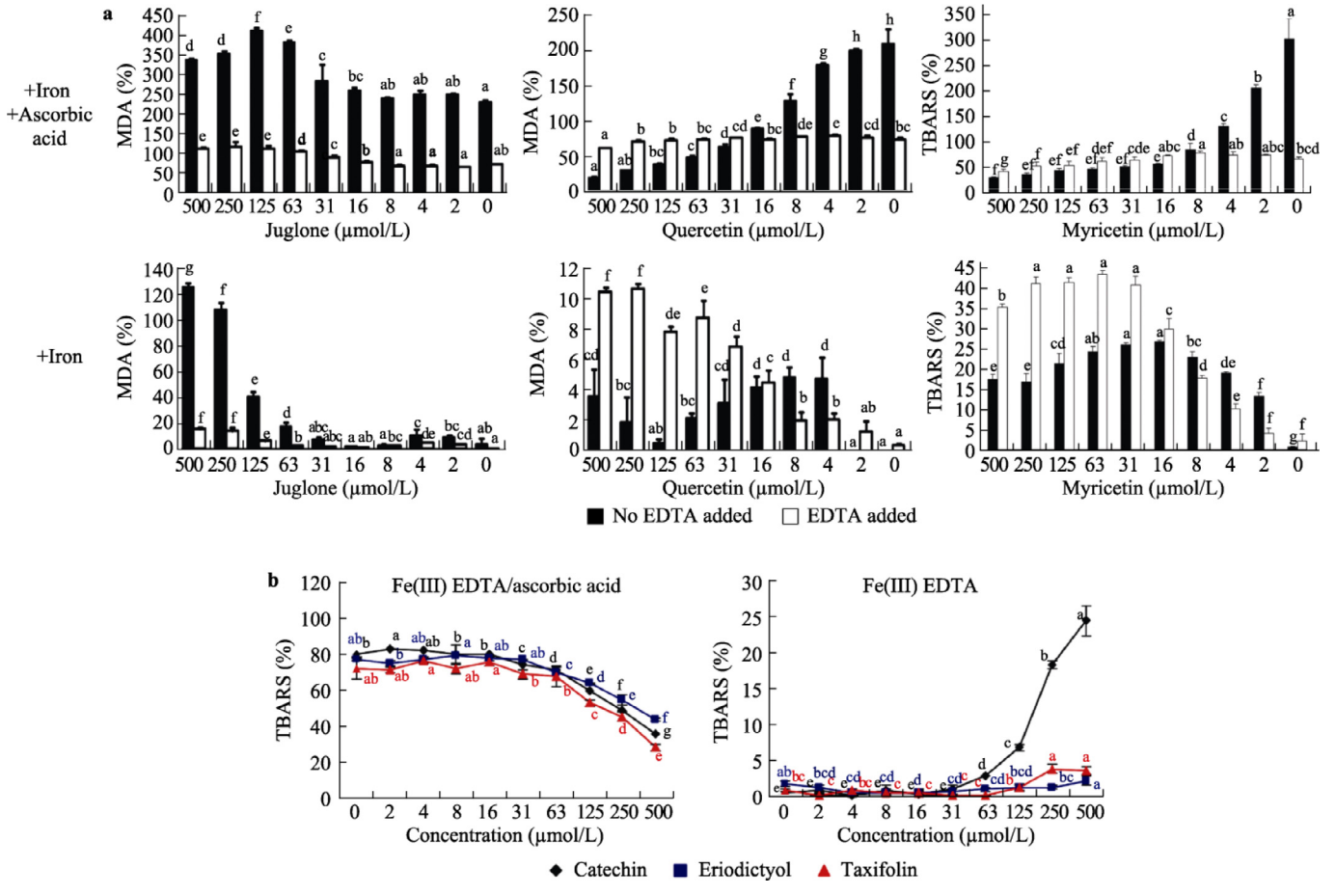

Fig. 5. Hydroxyl radical production was measured by deoxyribose degradation assay, followed by detection of degradation product malonyldialdehyde (MDA, %) or thiobarbituric acid-reactive species (TBARS, %). Pro-oxidant and antioxidant properties of (a) juglone, quercetin and myricetin in the presence/absence of EDTA. (b) catechin, eriodictyol, and taxifolin exhibit antioxidant properties except for catechin at high concentration. Very strong prooxidant properties, highly depending on free iron, can be seen by juglone. Figures taken and modified from Chobot, 2010, Chobot and Hadacek, 2011 and Chobot et al., 2016.

The mimosine-iron chelate complex may have increased membrane permeability and generate more reactive oxygen species than mimosine-alone. The strong similarity of mimosine to the essential amino acid tyrosine suggests a third means of toxicity. Nguyen and Tawata (2015) demonstrated improved inhibition of cellular tyrosinase and cyclooxygenase 1 by numerous mimosine dipeptides. Mimosine tetrapeptides exhibited five times the potency for influenza neuraminidase inhibition than mimosine alone (Upadhyay et al., 2011). Recently mimosine was shown to inhibit anticoagulatory activity of phospholipase A_2 in numerous snake venoms (Devi and Doley, 2020). Whether the true mode of enzyme inhibition be from metal chelation, binding site competition or a combination, leucaena trees have developed efficient means of handling incredibly high amounts (up to 10% dry weight) of mimosine in young growing tissue (Bageel et al., 2020).

6. Conclusions & future prospects

Plants have been relied upon as medicine for ages and yet new compounds continue to be discovered in species long recognized for their healing properties. As these new compounds are investigated, future studies should also consider the synergistic effects of flavonoid mixtures, as multiple mechanisms of action may produce potent antiviral effects. When used in combination with potent antiviral drugs, plant flavonoids can greatly magnify antiviral effects; demonstrated by genistein (LeCher et al., 2019), baicalein (Chen et al., 2011), and pomegranate extract (Haidari et al., 2009). Crude extract derived from *Houttuynia cordata* leaves produced more potent antiviral effects than treatments with individual flavonoids (Chiow et al., 2016). Modification of plant extract constituents or investigating plant extract mixtures may lead to potent treatments.

Anti SARS-coronavirus effects have been observed using *H. cordata* extract, which strongly activates cell-mediated immunity and directly inhibits essential viral enzymes (Lau et al., 2008). Indirect mechanisms of action by flavonoids, such as increasing nitric oxide (NOX) production, produce antiviral effects by inhibiting viral cysteine proteases (Saura et al., 1999). Depending on the concentration, environment, and compound, flavonoids may elicit NOX production yet also act as a NOX scavenger (Duarte et al., 2014). For example, glycyrrhizin was capable of suppressing coronavirus replication in vitro albeit requiring very high concentrations (Cinatl et al., 2003). Contrarily, in immunosensitive mice, low doses of glycyrrhizin more than doubled blood NO levels while higher doses had little effect (Li and Zhou, 2012). Effects may differ drastically whether in vitro or in vivo, however, plant polyphenols commonly exhibit little cytotoxicity in either case. Properly analyzing the medicinal applications of plant-based medicine requires that animal model studies receive special attention in the future.

Highly thorough reviews on flavonoid diversity and medicinal properties can be found for *Sophora* spp. (Krishna et al., 2012; Aly et al., 2019), *Morus* spp. (Wei et al., 2016), and *Morinda* spp. (Singh and Sharma, 2020) yet only few examples may be found in these reviews which include antiviral effects. Considering the massive social disruption caused by the 2019 coronavirus pandemic, demand for new antiviral strategies can be expected to fuel growth in medicinal phytochemistry.

Declaration of Competing Interest

There are no conflicts to declare.

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