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Update on Phytochemical and Biological Studies on Rocaglate Derivatives from *Aglaia* Species

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Abstract

Aglaia, with about 120 species, is one of the largest genera of the plant family Meliaceae (the mahogany plants), and is native to the tropical rainforests of the Indo-Australian region, ranging from India and Sri Lanka eastwards to Polynesia and Micronesia. Various *Aglaia* species have been investigated since the 1960s for their phytochemical constituents and biological properties, with the cyclopenta[*b*]benzofurans (rocaglates or flavaglines) being of particular interest. Phytochemists, medicinal chemists and biologists have conducted extensive work in establishing these secondary metabolites as potential lead compounds with antineoplastic and antiviral effects, among others. The varied biological properties of rocaglates can be attributed to both their unusual structures and their ability to act as inhibitors of the eukaryotic translation initiation factor 4A (eIF4A), hence affecting protein translation. The present review provides an update on the recently reported phytochemical constituents of *Aglaia* species, focusing on rocaglate derivatives. Furthermore, laboratory work performed on investigating the biological activities of these chemical constituents is also covered.

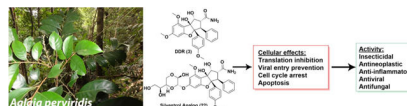
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Dedicated to Professor Arnold Vlietinck in recognition of his important contributions to natural product research on the occasion of his 80th birthday in 2021.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Graphical Abstract



Keywords

Aglaia; Meliaceae; natural products; rocaglates; flavaglines; rocaglamide; silvestrol; biological effects; antineoplastic activity; antiviral activity; protein translation inhibition

Introduction

Since the first phytochemical report of the tetracyclic triterpene, aglaiol, from the leaves of the oriental plant *Aglaia odorata* in 1965 [1], many studies have appeared describing the chemical constituents of *Aglaia* species in terms of elucidating the structurally diverse natural products present. Examples of secondary metabolite compound classes isolated from *Aglaia* species include bisamides [2–4], flavonoids [2, 5], lignans [6], and triterpenoids, particularly of the baccharane, cycloartane, and dammarane types [7–9]. In addition, more than 100 biogenetically related oxygen-containing heterocyclic secondary metabolites have been isolated to date, and are characteristic of many *Aglaia* species, and are known collectively as rocaglamide (**1**) derivatives. Such compounds have been divided into three sub-classes: (i) cyclopenta[*b*]benzofurans (CPBFs; “flavaglines” or “rocaglates”); (ii) cyclopenta[*b*]benzopyrans (“thapsakins” or “aglain” derivatives) and (iii) benzo[*b*]oxepines (“thapoxepines” or “forbaglines”), which are considered to be formed by the cycloaddition of a cinnamic acid amide and a flavonoid unit [10, 11]. Of these three groups, rocaglates are the most potently bioactive and well-investigated chemical constituents of *Aglaia* species and thus the main focus of the present article.

(–)-Rocaglamide (**1**), a CPBF, was the first compound obtained in its class and was isolated in 1982 from the dried roots and stems of *Aglaia elliptifolia* as an *in vivo*-active antileukemic agent [12]. In subsequent years, more than 60 rocaglate derivatives have been isolated and structurally identified from several *Aglaia* species [13, 14]. With most substitutions occurring at the C-1 and C-2 positions of their phenyl rings (Fig. 1), some examples of rocaglate derivatives are methyl rocaglate (**2**) [15, 16], didesmethylrocaglamide (DDR, **3**) [13, 15], rocaglaol (**4**) [17], aglaroxin C (**5**) [18], cyclorocaglamide (**6**) [19], and isothapsakon A (**7**) [20]. Another rocaglate derivative that has garnered much scientific attention is silvestrol (**8**), which was isolated and structurally characterized along with its 5^{'''}-epimer, episilvestrol (**9**) [21]. These two rocaglate congeners were purified from the stem bark of *Aglaia foveolata* (originally misidentified taxonomically as *Aglaia silvestris*) collected in Indonesia, and contain an unprecedented dioxanyl ring connected to the CPBF core at the C-6 position of the phenyl ring A (Fig. 1). The presence of a dioxanyl ring was demonstrated to enhance the cytotoxic potency of rocaglates [2, 22, 23] and has led to extensive work on the synthesis and structure-activity requirement exploration of rocaglamide, silvestrol, and related analogues [22–28].

A pivotal paper exploring the cellular mechanism of activity of the rocaglates was published in 2008 [29], in which Pelletier and his associates reported silvestrol as an inhibitor of protein translation by modulating the activity of the eukaryotic initiation factor (eIF) 4A, an RNA helicase subunit of the eIF4F complex. This work has been complemented by further mechanistic reports from the same group [30, 31], with selected rocaglates also being documented to act at the cellular level to modulate the Raf-MEK-ERK pathway via targeting prohibitins (PHBs) 1/2 [32], MAPK [33], and FMS-like receptor tyrosine kinase 3 (FLT3) and the microRNA-155 (*miR-155*) gene [34]. Such biological studies have laid the foundation for developing rocaglamide and silvestrol as potential drug leads against different disease states including, in particular, cancer, and more recently, certain viruses.

This review describes the work on rocaglates from *Aglaia* species, primarily in terms of their phytochemical isolation, structural characterization, and biological activities, as reported during the period 2014–2020. It is intended as an update of the two previous review articles we wrote on this same topic in 2006 [22] and 2014 [23], and includes experimental contributions from the respective laboratories of the three current senior authors. Additionally, a summary is included of the collection of several *Aglaia* species from three Southeast Asian countries (Indonesia, Laos and Vietnam) under various formal Memoranda of Agreement (MOA) with the University of Illinois at Chicago, as part of two multi-institutional collaborative research projects funded by the U.S. National Cancer Institute (NCI) [35–37]. To assist with the writing of this review, the SciFinder literature database (Chemical Abstracts Service, Columbus, OH, USA) was searched using keywords such as *Aglaia*, rocaglamide and silvestrol and then categorized and refined for relevant publications and patents from 2014 onwards.

Taxonomy and Collection

The genus *Aglaia* is a large group of plants, mostly comprised of trees, belonging to the family Meliaceae. These species have a natural distribution spanning the tropics from Sri Lanka and India, east to the Pacific through Burma, southern mainland China, Taiwan, Vietnam, Malaysia, Indonesia, the Philippines, New Guinea, Northern Australia, and the Western Pacific. In the volume “A Taxonomic Monograph of The Genus *Aglaia* Lour. (Meliaceae)”, Dr. Caroline Pannell (University of Oxford, Oxford, UK), a leading taxonomic specialist of this genus, included 104 species as belonging to *Aglaia* [38]. However, today, approximately 120 *Aglaia* species are recognized [39]. The largest concentration of this genus is found in Indonesia, followed by Malaysia, the Philippines, and the Indochina region (including Thailand and southern mainland China). In the taxonomic system, *Aglaia* belongs to the Tribe Aglaieae, within the Subfamily Melioideae and is made up of two taxonomic sections, namely, the Section *Aglaia* and the Section *Amoora* [38]. In 2005, based on a phylogenetic study, Muellner and coworkers [40] recognized three taxonomic sections within the genus, viz., the Sections *Amoora*, *Neoaglaia*, and *Aglaia*, which are defined morphologically primarily by their fruit characteristics and by the numbers of flower parts.

All species of *Aglaia* are woody, ranging in size from a few meters high to large trees up to 40 m tall. The bark of these trees and their branches tend to exude a sticky white latex when incised. Most species have imparipinnate leaves, although these are occasionally simple

or trifoliolate. Characteristically, branchlets and leaves are covered by an indumentum of peltate scales or stellate hairs, which may be used to identify certain species. The flowers of the members of the genus are small (1–10 mm long) and subglobose or ellipsoid and unisexual, normally set in a terminal and axillary paniculate inflorescence. In classifying the species, the staminal tube in the female flower provides the most taxonomic information. The fruits are either ellipsoid, obovoid or pear-shaped, dehiscent or indehiscent and covered by a stellate type of scales or hairs, with the pericarp thick and pliable. The outer layer of the seed coat (referred to as the aril) is usually fleshy [38].

Members of the genus *Aglaia* are found growing in both evergreen and monsoon primary and secondary forests, from sea level to an altitude of 1,500 m, or rarely higher, and occur mostly in evergreen forests and less commonly in monsoon forests. *Aglaia* species populations are normally scattered, not in a dense and dominant cluster, and many species have become rare due to forest clearance and may be threatened. Examples include *A. foveolata*, *A. spectabilis* and *A. perviridis* [41]. Most species yield good hardwood timber that can be used in construction, such as for buildings, bridges, houses, and furniture. Several species have found traditional medicinal uses, especially the leaves, for the treatment of bodily afflictions, such as wounds, fever, headache, asthma, jaundice, and as a tonic, e.g., after childbirth [42, 43]. One species, *A. odorata*, often found in cultivation, has a history of wide use in systems of traditional medicine to treat various diseases [44, 45].

During the time of operation of the two NCI supported multi-institutional research projects [35–37], a total of 17 identified species of *Aglaia* were collected for investigation for potential anticancer activity (Table 1). The greatest number of collections came from Indonesia (11 species), while a small number came from each of Laos (three species), Vietnam (two species), and Thailand (one species). Voucher specimens of these collections are in deposit at the Herbarium of the Field Museum of Natural History, Chicago, IL, USA, as well as at herbarium institutions in the county where each collection was made.

Phytochemical Reports of Rocaglate (Cyclopenta[*b*]benzofurans) Constituents of *Aglaia* Species (2014–2020)

In 2014, our group at The Ohio State University (OSU) published a comprehensive review focusing on rocaglamide (**1**), silvestrol (**8**), and their structurally related bioactive compounds [23], inclusive of isolation of several new rocaglates from four *Aglaia* species (*Aglaia cucullata*, *A. edulis*, *A. odorata*, and *A. perviridis*). Recent reports published largely during the period 2014–2020 have described the isolation of new rocaglate derivatives from only a relatively few *Aglaia* spp., namely, *A. odorata*, *A. oligophylla*, *A. perviridis*, and *A. stellatopilosa*. Many of the research reports on the *Aglaia* CPBFs published over the last few years have focused on their syntheses, analogue development and biological activity evaluation, with the last-mentioned topic, in particular, to be covered in subsequent sections of this review.

In 2015, An et al. reported the structures of eight new benzo[*b*]oxepine derivatives, aglaodoratins A-H [46], and eight new cyclopenta[*b*]benzopyrans, biosynthetic precursors to rocaglates, aglapervirisins B-J [47], from the leaves of *Aglaia odorata* and *Aglaia perviridis*,

respectively. Of these 16 secondary metabolites, aglaodoratins C (**10**), D (**11**) and E (**12**) (Fig. 2) were observed to exhibit moderate cytotoxicity, with their IC₅₀ values in the range from 0.097 to 6.25 μM, against three human cancer cell lines (HT-29 colon cancer, SMMC-7721 hepatocellular cancer, and MG-63 osteosarcoma). Additionally, aglaodoratin C (**10**) inhibited cellular proliferation by arresting cells at the G2/M cell-cycle phase and thereby inducing apoptosis in HepG2 liver cancer cells *in vitro* [46]. In contrast, aglapervirins B-J were either only weakly active or non-cytotoxic for a panel of four human cancer cell lines [47]. Interestingly, Kong and colleagues recently published a further phytochemical investigation on the leaves of *A. perviridis*, where they reported four new aglain glycosides (aglapervirins J-M) with weak anti-inflammatory activity, as determined by an *in vitro* nitric oxide inhibition assay using the RAW264.7 mouse macrophage tumor cell line [48].

Two separate groups reported the similar compounds rocaglamide AY (**13**) [49] and aglaodoratin I (**14**) [46], isolated from the leaves of *A. oligophylla* and *A. odorata*, respectively. Both these rocaglates have an oxime group at the C-1 position but aglaodoratin I (**14**) possesses a hydroxy group at the C-3' position instead of a hydrogen atom, as seen in rocaglamide AY (**13**) (Fig. 2). The limited quantity of **14** obtained prevented it from being evaluated for cytotoxicity [46]. Although no biological test results were reported for rocaglamide AY (**13**) either, it was mentioned that many rocaglamide congeners possess insecticidal properties against the insect agricultural pest, *Spodoptera littoralis* [49]. Another paper published in 1999 reported a similar compound **15**, also from the twigs and leaves of *Aglaia odorata*, which exhibited moderate insecticidal activity (LC₅₀ of 1.3 ppm) toward *Spodoptera littoralis* larvae [10]. Additionally, a rocaglaol derivative **16**, with a formamide group at the C-1 (*S*) position and a bromine at C-4' instead of a methoxy group, was found to have cytotoxic activity ranging from 0.5–2.3 nM against an array of human cancer cell lines [50], suggesting an amide at C-1 may lead to a more potent cytotoxic effect when compared to rocaglate derivatives with a more typical hydroxy group found at this position.

In 2016, Othman and colleagues published the isolation of silvestrol (**8**) and its epimer 5'''-episilvestrol (**9**), in addition to several new 2,3-seco-dammarane triterpenoids, from the stems of *Aglaia stellatopilosa*, collected in Sarawak, Malaysia [51]. Earlier, silvestrol (**8**) was reported in a patent application as an antineoplastic constituent of the Malaysian plant *Aglaia leptantha*, which was later re-identified as *A. stellatopilosa* [52]. However, the structures for the isolated compound described in this patent did not show full configurational details, and did not distinguish between compounds **8** and **9**. Silvestrol (**8**) and episilvestrol (**9**) were also purified from the leaves of *Aglaia perviridis* in 2016, collected in Yunnan Province of the People's Republic of China [47]. Moreover, our group confirmed the presence of compounds **8** and **9** in a root sample of *A. perviridis* collected in Vietnam [53]. Therefore, to date, cyclopenta[*b*]benzopyrans containing a dioxanyl ring as in silvestrol (**8**) have been found in only three of the approximately 120 *Aglaia* species (i.e., *A. foveolata*, *A. perviridis*, and *A. stellatopilosa*), making them rare constituents of this genus.

In addition to episilvestrol (5'''-episilvestrol) (**9**), a small number of additional structural modified variants of silvestrol (**8**) have been reported from *Aglaia* species. In 2010, as a result of a large-scale recollection of the stem bark of *A. foveolata* from Kalimantan,

Indonesia, the compounds 2''''-episilvestrol and 2''',5''''-diepisilvestrol were obtained as trace constituents, with both having reduced cytotoxic potencies when compared to silvestrol [8]. As a result of this work, which utilized specialized large-scale isolation facilities available at NCI, a sufficient amount of silvestrol (ca. 100 mg) was purified from the recollected plant material in order to conduct extensive biological testing at OSU and elsewhere [34, 54, 55]. An et al. in 2016 reported aglapervirisin A (**17**) as a new silvestrol analogue with an acetate group at the C-6''' position of the dioxanyl ring side chain (Fig. 2) [47]. Cytotoxic profiling of aglapervirisin A (**17**) in four human cell lines (HT-29 colon cancer, HepG2 hepatocarcinoma, HL-60 leukemia, MCF-7 breast cancer) showed that it had comparable potencies to silvestrol (**8**) and episilvestrol (**9**), with IC₅₀ values ranging from 8–14 nM. Further mechanistic evaluation of **17** against HepG2 cells, uncovered the ability of this mono-acetylated molecule to lower the expression levels of tyrosine phosphatases, Cdc2, and Cdc25, thereby causing apoptosis by arresting cells at the G2/M phase [47].

In 2019, our group at OSU reported five new cyclopenta[*b*]benzofuran analogues (**18–22**) from the leaves of *Aglaia perviridis* collected in the Nui Chua National Park in Vietnam [53]. Of these compounds, **18–21** were observed to have a fused dihydrofuran ring to both the dioxanyl and aryl rings of the rocaglate core (Fig. 2) and an amide moiety at C-2. Compound **22**, elucidated as a 2'''-hydroxy derivative of episilvestrol (**9**) with an amide moiety at C-2, was isolated as an enantiomeric mixture (Fig. 2). Of these isolates, only compound **22** exhibited low micromolar cytotoxic potency against the human colon (HT-29) and prostate cancer (PC-3) cell lines. However, this study provided some structure-cytotoxic activity information, in that a hydroxy group at C-2''' and the rigidity in structure between the dioxanyl and CPBF core might be detrimental to the cytotoxic activity of these flavaglines [53].

In the most recent report on *Aglaia perviridis* by Kong and colleagues [48], a novel rocaglate derivative was described, (±) aglapernin (**23**), which did not show cytotoxicity against cancer cell lines, but exhibited weak antibacterial activity (125 μM) against *Porphyromonas gingivalis*.

Another recent development worthy of mention, is the silvestrol-based antibody drug conjugates (ADCs), developed in 2017 by Genentech, Inc. [56]. ADCs are target-specific prodrugs, with a warhead (the cytotoxic drug) connected to a specific antibody via a linker [57–59]. The warhead bioactive moiety of the ADC provides the biological activity to the macromolecule, in antibody-targeted cells. In their patent, the Genentech team synthesized various silvestrol-ADC analogues, incorporating a dioxanyl ring system, with different antibodies. These ADCs were then evaluated both *in vitro* and *in vivo*, in breast cancer cells and B-cell malignancies. Silvestrol-ADCs connected to cysteine modified CD22 antibodies demonstrated promising results against a CD22-expressing xenograft mouse model [56].

Therapeutic Potential of Rocaglates (Update 2014–2020)

Since the initial report of rocaglamide (**2**) from *Aglaia elliptifolia* as an antileukemic agent in the early 1980s [12], the therapeutic potential of CPBFs has been evaluated and reported by a number of research groups. The diverse range of biological activities

evaluated for these compounds have included antineoplastic, insecticidal, anti-inflammatory, neuroprotective, and more recently, antiviral properties [2, 22, 23, 60]. Fig. 3 gives a graphical representation of the published work on these compounds over the period 2014–2020. Continued modifications of the functional groups at specific positions have contributed to a better understanding of the structure-activity relationships of rocaglates as potential therapeutic agents. Substantial work has been conducted in establishing their biological targets, of which two have been explored to the greatest extent, namely, eIF4A [29, 30, 61] and PHB1/2 [32, 62, 63].

The initial studies exploiting the cellular mechanistic action of silvestrol (**8**) were published just a few years after its isolation, where it was observed to influence the interaction between eIF4A and RNA [29, 30]. This work was followed by the demonstration of synthesized biotinylated 5''-episilvestrol to selectively inhibit eIF4A/II [26].

Over the last few years, several studies have been published from our collaborative work on the effects of various rocaglate derivatives against a number of neurofibromatosis-associated tumors and pediatric sarcomas, with the biological testing experimental work performed at the Nationwide Children's Hospital, Columbus, Ohio, USA. In an initial study using silvestrol (**8**), it was shown that the eIF4F components, including eIF4A, are potential therapeutic targets in malignant peripheral nerve sheath tumors (MPNSTs) and vestibular schwannomas [64]. Genetic depletion of eIF4A using short-hairpin RNAs and pharmacological inhibition using the natural eIF4A inhibitor silvestrol potently suppresses the growth of MPNSTs and schwannomas by decreasing the levels of multiple mitogenic signaling molecules including AKT, ERKs, Aurora A, and cyclins, important for tumor growth. The decrease of tumor growth was correlated with elevated levels of phospho-histone H3 and with G₂/M arrest and apoptosis observed in the tumor cells treated with silvestrol [64].

The inhibition of the overexpressed eIF4F components in meningiomas was also investigated using a panel of 23 natural products, inclusive of representatives of the cucurbitacin, diarylheptanoid, rocaglate, simaroubolide, stilbenoid, sesquiterpene lactone, and xanthone structural classes [65]. Of the compounds examined, silvestrol (**8**) and episilvestrol (**9**) were the two most growth-inhibitory compounds, with silvestrol being more potent (IC₅₀ 10 nM) than episilvestrol (IC₅₀ 32 nM) against *NF2*-deficient meningioma Ben-Men-1 cells. Like in MPNSTs and schwannoma cells, silvestrol (**8**) treatment induced G₂/M arrest in the meningioma cells. Taken together, it was suggested that inhibiting protein translation is a potential treatment approach for for MPNSTs, schwannomas, and meningiomas, including those associated with neurofibromatosis [64, 65].

However, silvestrol (**8**) has suboptimal drug-like properties, including a bulky structure, poor oral bioavailability [66], and sensitivity to multi-drug resistance 1 (MDR1) efflux [67]. Moreover, a toxicity study in larger animals conducted by our colleagues and collaborators at OSU and the NCI Developmental Therapeutic Program (DTP) revealed toxic effects of silvestrol in the lungs of dogs [68]. Consequently, further development of silvestrol as a cancer therapy was suspended. To search for compounds with better drug-like properties, alternative rocaglate congeners to silvestrol (**8**) were sought as potential

growth inhibitors of MPNST, schwannoma and meningioma cells [68]. Upon side-by-side comparison of ten rocaglates lacking the dioxanyl ring with silvestrol (**8**), rocaglamide (**1**) and DDR (**3**) were found to exhibit growth-inhibitory activity comparable to silvestrol (**8**). Like silvestrol, both rocaglamide (**1**) and DDR (**3**) arrested tumor cells at G₂/M, and induced apoptosis and a DNA-damage response, while decreasing the expression of multiple mitogenic kinases, consistent with translation inhibition. In collaboration with colleagues at the NCI DTP, rocaglamide (**1**) was observed to be 50% orally bioavailable and did not show any discernible pulmonary toxicity in dogs. In addition, both rocaglamide (**1**) and DDR (**3**) were not sensitive to MDR1 inhibition, possibly due to the lack of a dioxanyl ring. Most importantly, when administered either intraperitoneally or orally, rocaglamide (**1**, NSC326408) potently inhibited tumor growth in an orthotopic MPNST model. In addition, rocaglamide (**1**) exhibited broad antitumor activity in patient-derived xenograft (PDX) models for a Ewing sarcoma, an osteosarcoma, and an alveolar rhabdomyosarcoma. In a comparative *in vitro* study of 11 rocaglate congeners, including rocaglamide (**1**), methyl rocaglate (**2**), DDR (**3**), rocaglaol (**4**), and silvestrol (**8**), DDR (**3**, IC₅₀ between 5 and 15 nM) was found to be the most potent compound, when tested against a panel of MPNST, a schwannoma, and a meningioma cell lines [68]. (–)-DDR (**3**) was obtained earlier in our work as a trace constituent from the combined leaves, twigs and fruits of *Aglaia perviridis* when collected in Vietnam, and differs from rocaglamide (**1**) in possessing an amide unit instead of a dimethylamide functionality at the C-2 position of the CPBF core (Fig. 1) [13]. In a follow-up investigation, chemically synthesized DDR (**3**) was also found to effectively block tumor growth in orthotopic cell line-derived xenograft (CDX) and PDX models of osteosarcoma [69]. It was suggested that both rocaglamide (**1**) and DDR (**3**) are worthy of further evaluation as potential treatments for pediatric bone and soft-tissue sarcomas.

Additional studies have been performed on the cellular mechanism of action of rocaglate family members as eIF4A inhibitors. Chu and colleagues used CRISPR-Cas9 as a tool for drug-target validation *in vivo*. They validated the rocaglate-eIF4A relationship by introducing an eIF4A1 mutant allele (F163L) into cells and showed that eIF4A1(F163L) retains helicase activity but was unresponsive to rocaglates, such as silvestrol (**8**) [70]. Iwasaki et al. reported that rocaglamide (**1**) does not repress translation of specific messenger RNAs by reducing cellular eIF4A availability, but rather by clamping eIF4A onto the polypurine sequences in an ATP-independent manner [71]. This same group later elucidated the crystal structure of a complex of human eIF4A-rocaglamide-polypurine RNA, and showed rocaglamide to target a bimolecular cavity between eIF4A and polypurine RNA [72]. Recently, Sidraharan et al. treated breast cancer stem cells (BCSCs) with rocaglamide (**1**), determining eIF4A as a valid molecular target for both BCSCs and bulk tumor cells. They further suggested that eIF4A inhibitors may be combined synergistically with existing chemo-, radio- and/or immunotherapies [73].

Extensive follow-up work has been done more recently since an initial documentation of rocaglates and their inhibitory effect on PHB1/2 [32]. This includes not only the investigation of their antineoplastic activity but also their potential antiviral effects. Liu and colleagues evaluated rocaglamide (**1**) and aglaroxin C (**5**) in hepatitis C virus (HCV)-infected human hepatoma cells [63]. HCV, responsible for hepatitis C and liver cancer in

humans, enters human hepatocyte cells utilizing different membrane proteins, particularly based on the interaction between its glycoprotein E2 and PHB1/2 [74]. Rocaglamide (**1**) inhibits HCV entry into human hepatoma cells by targeting PHB1/2, which in turn inhibits the CRaf/RAS pathway, an integral component in cell proliferation and signaling [75]. While synthesized aglaroxin C (**5**, Fig. 1) was found to exhibit a weak effect on HCV replication or entry into cells, several further analogues of **5** were shown to be more effective HCV entry inhibitors, including **24** and **25**, in which the C-aryl group of the pyrimidinone is differentially substituted [76, 77]. These two compounds exhibited low cytotoxicity ($EC_{50} = 0.5 \mu\text{M}$), 3-fold greater in comparison to aglaroxin C (**5**), against human hepatoma Huh-7.5.1 cells infected with HCV and were suggested to inhibit viral entry rather than replication as their mechanism of action [76]. Another similar study with enterovirus 71 (EV71), responsible for hand, foot, and mouth disease in humans, demonstrated a dependence on PHB for cell entry, with rocaglamide (**1**) used to investigate EV71 translation and entry inhibition [78]. An *in vivo* study of EV71-infected mice showed that mice survived longer with lower viral loads in the brain and spinal cord, on treatment with rocaglamide (**1**, 0.25 mg/kg), as compared to those treated with vehicle (0.25% DMSO in olive oil). These data were supported by an *in vitro* study of EV71-infected motor-neuron NSC-34 cells, where a dose-dependent reduction in viral load was observed in cells treated with rocaglamide (**1**, 10–100 nM) [78].

In 2017, silvestrol (**8**) was evaluated *in vitro* for its antiviral activity against the Ebola virus (EBOV) [79]. This study by Biedenkopf et al. demonstrated the ability of silvestrol (**8**) to inhibit EBOV infection at a low non-cytotoxic concentration (10 nM). Additionally, they demonstrated that reduction of EBOV propagation correlated with the disappearance of viral nucleoprotein (NP), which is comparable to translational inhibition of PIM1, a cellular kinase known to be affected by silvestrol (**8**) [79]. In another antiviral study, Slaine et al. examined the role of silvestrol (**8**) in blocking the replication of influenza A virus (IAV) [80]. They showed that silvestrol treatment during early IAV infection induced stress granule formation, inhibited viral protein synthesis, and blocked viral replication. Interestingly, the viral protein synthesis was “recovered” upon silvestrol (**8**) withdrawal, suggesting a reversible translation inhibition mode of action [80].

Several further evaluations of rocaglamide (**1**) and silvestrol (**8**) as potential antiviral agents have been performed against hepatitis E virus (HEV) [81, 82], corona- and picornaviruses [83], chikungunya virus [84], Ebola virus and Marburg virus [85] and zika virus [86]. All these studies were based on the assumption that efficient translation of the mRNAs of these viruses, which contain highly structured 5'-untranslated regions (5-UTRs), requires the DEAD-box RNA helicase eIF4A. (–)-CR-31-B (**26**), a synthesized rocaglate hydroxamate, was evaluated by Müller and colleagues for its antiviral activity against HEV, corona-, zika-, Lassa- and Crimean Congo hemorrhagic fever viruses, in comparison with silvestrol [87]. It was found that (–)-CR-31-B (**26**) exhibited slightly more potent viral inhibition than silvestrol (**8**), with EC_{50} values in the low nanomolar range for most of the viruses examined. However, the inhibitory activity of (–)-CR-31-B (**26**) against HEV replication was somewhat weaker in comparison to silvestrol (**8**), suggesting a potential difference in the antiviral mode of action between these two rocaglates [87]. Recently, the synthetic

rocaglate (–)-CR-1–31-B (**26**) was employed to show that eIF4A is a therapeutic target in pancreatic duct adenocarcinoma (PDA), and it suppressed tumor growth and extended the survival time in a genetically engineered mouse PDA model [88].

Two additional mechanistic targets of rocaglates have been suggested, namely, KRAS [89], a member of the RAS family of a small GTPases, and DDX3, a DEAD-box RNA helicase [90]. RAS proteins are imperative for triggering multiple signaling pathways required for cell proliferation and survival [91]. Mutations in *KRAS*, have been frequently found in several types of cancer, including pancreatic, lung, and colon cancers, and non-small-cell lung carcinoma [92]. According to Yurugi et al., flavaglines, particularly rocaglamide (**1**), potentially inactivate RAS by inhibiting its GTP loading, and deterring its nanocluster formation at the phospholipid-enriched sites on the plasma membrane [89]. In turn, Chen et al. [90] focused on DDX3, a highly conserved DEAD-box helicase involved in cell-cycle regulation, differentiation, survival, and apoptosis [93]. Rocaglamide (**1**) was discerned to clamp DDX3 on its polypurine sequences in an ATP-independent manner, and the glutamine at position 360 was found to be a critical residue for DDX3 binding by this rocaglate [90].

Other Biological Properties of Rocaglate Derivatives

In 1985, Chiu published an initial report of the antifeedant activities against three agricultural pests of an acetone extract of *Aglaia odorata* [94]. This was followed up in 1993 by the work of Ishibashi and colleagues showing that two CPBF constituents, rocaglamide (**1**) and methyl rocaglate (**2**), from this plant demonstrated potent insecticidal activities against the larvae of the variegated cutworm (*Peridroma saucia*) [16]. Subsequently, several studies have evaluated the potential insecticidal effects of rocaglamide and its analogues. Although the exact mechanism of action for the insecticidal property of CPBFs is as yet unknown, phytochemists and medicinal chemists have obtained several congeners to evaluate their structure-activity relationships. For instance, the free hydroxy groups at both C-1 (*R*) and C-8b were essential for mediation of the insecticidal activity of rocaglamide (**1**) (Fig. 1), when evaluated against the pest insect *Spodoptera littoralis* [95, 96]. Moreover, favorable modifications by chemical synthesis at C-2 or C-4' for insecticidal activity are a hydroxamide and halogen (Br or Cl) functional group, respectively. Such derivatives were well-tolerated in comparison to rocaglamide (**1**), and exhibited LC₅₀ values ranging from 3 to 12.5 mg/L against an array of pests and beetles inclusive of *Diabrotia balteata*, *Heliothis virescens*, *Plutella xylostella*, and *Spodoptera littoralis* [97].

Treatment of cerebral malaria, caused in particular by infection of *Plasmodium falciparum*, has proven to be a continued challenge. In spite of the widely available synthetic analogs of the plant-derived sesquiterpene lactone, artemisinin, resistance to this compound class by the causative organisms has been observed [98, 99]. Langlias and associates recently suggested the possibility of using rocaglates as potential therapeutic intervention agents for malaria. They showed the synthetic rocaglate derivative (–)-CR-31-B (**26**) to exhibit antiplasmodial activity. According to their report, owing to its potential to inhibit eIF4A, (–)-CR-31-B (**26**) not only inhibited *Plasmodium* protein synthesis at low nanomolar levels (ranging between 0.9 and 2.8 nM) *in vitro* but also showed similar effects in a dose-dependent manner in mice infected with *Plasmodium berghei* [100]. Additionally, their

study highlighted the anti-inflammatory activity of (–)-CR-31-B (**26**) by suppressing the production of interferon regulatory factor 1 (IRF1), a pro-inflammatory transcription factor important for the expression of critical inflammatory factors, like GBP2 and CXCL10 [100]. Complemented with a previous study that established good pharmacokinetic properties of this synthetic rocaglate [101], Langlais et al. proposed that (–)-CR-31-B (**26**), warrants further evaluation as a potential therapy for cerebral malaria, either as a single agent or in combination with artemisinin [100].

In a recent publication, Wang et al. evaluated the potential neuroprotective effects of a 95% ethanol extract of *A. odorata* leaves [102]. This plant extract was found to exhibit a neuroprotective effect in a middle cerebral artery occlusion (MCAO) rat model. Treatment with this extract reduced the number of apoptotic cells and increased mitochondrial membrane potential in oxygen-glucose deprivation/reperfusion (OGC/R)-induced PC12 cells. It was hypothesized that the extract exerts a neuroprotective effect against cerebral ischemia by suppression of the p53/Puma mediated signaling pathway [102]. While these biological results look interesting, the investigation was not supported by any detailed phytochemical work, but only with a preliminary chromatographic profiling method indicating the presence of triterpenoids in the extract [102]. It is possible that the actual active constituents may include rocaglate derivatives, as already reported from *A. odorata* [16, 46].

Conclusions

Unlike many other structural classes of specialized metabolites from higher plants that have long been known, the novel rocaglate (flavagline) derivative, (–)-rocaglamide (**1**), was first reported in 1982 from the leaves of *Aglaia elliptifolia* [12]. At the time of its isolation, the structure and absolute configuration of this CPBF were determined by single-crystal X-ray crystallographic analysis, and it was shown to exhibit antileukemic activity (T/C value of 156%) in a P388 murine leukemia *in vivo* assay at a non-toxic dose (1.0 mg/kg) [12]. Likewise, the antileukemic activity of the dioxanyl-ring containing CPBF (–)-silvestrol (**8**) was reported in 2004 from *Aglaia foveolata*, and its full structure and stereochemistry were determined also by X-ray diffraction analysis [21]. Dioxanyl ring-containing CPBFs are rare constituents in *Aglaia* species, and, at the present time they have been found in only three of the approximately 120 members of this genus [8, 21, 47, 51–53]. Subsequently, and particularly over the last decade, the key cellular mechanism inhibition of eIF4A [29, 30] and PHB1/2 [32] has made rocaglamide (**1**) and silvestrol (**8**) of wide interest to the biomedical community as standard protein translation inhibitors. Both these compounds are now available commercially from fine-chemical scientific suppliers for research use. As a potential means of increasing their supply, rocaglamide [103–106] and silvestrol [107, 108] have been subjected to total chemical synthesis. In addition, methods have been developed for synthesizing rocaglate analogues to establish further structure-activity relationship information [109, 110]. However, it should be reiterated that while silvestrol has proven to be a useful pharmacological tool, it has sub-optimal drug-like properties and can cause pulmonary toxicity [68]. Therefore, this dioxanyl ring-containing natural product needs to be modified structurally for further development as a bioactive molecule drug lead.

Several review articles have appeared recently by various groups on the pharmacological activities of rocaglates, and have dealt, in particular, with their antineoplastic [14, 25, 111], antiviral [111, 112], and miscellaneous biological effects [14]. In terms of drug development, work on a synthetic derivative of rocaglamide (**1**), eFT-226 (**27**, Zotatfin), which was elucidated to have good pharmacokinetic properties and potent antitumor effects, like rocaglamide (**1**) and DDR (**3**), seems promising. The potent eIF4A inhibitor, Zotatfin, is the first compound with this mechanism of action to have entered into a clinical trial, as a potential treatment for patients with advanced solid-tumor malignancies [113].

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ABBREVIATIONS

5'-UTRs 5'	untranslated regions
ADC	antibody-drug conjugate
AMPPNP	adenylyl-imidodiphosphate
BCSCs	breast cancer stem cells
CDX	cell line-derived xenograft
CPBF	cyclopenta[<i>b</i>]benzofuran ring system
DDR	didesmethylrocaglamide
DDX3	DEAD-box RNA helicase 3
EBOV	Ebola virus
eIF4A	eukaryotic initiation factor 4A
EV71	enterovirus 71
FLT3	FMS-like receptor tyrosine kinase 3
HCV	hepatitis C virus
HepG2 cells	human hepatoblastoma cell line
HEV	hepatitis E virus
IGF-1	insulin-like growth factor-1
IRF1	interferon regulatory factor 1
MDR1	multi-drug-resistance protein 1
MPNST	malignant peripheral nerve sheath tumor

NSCLC	non-small-cell lung carcinoma
p53/Puma	p53 upregulated modulator of apoptosis
PC-3	prostate cancer cell line
PDA	pancreatic ductal adenocarcinoma
PDX	patient-derived xenograft
PHB1/2	prohibitins 1 and 2
PIM1	proto-oncogene serine/threonine-protein kinase
Raf-MEK-ERK	mitogen-activated protein kinases (MAPKs) involved in cell proliferation and survival

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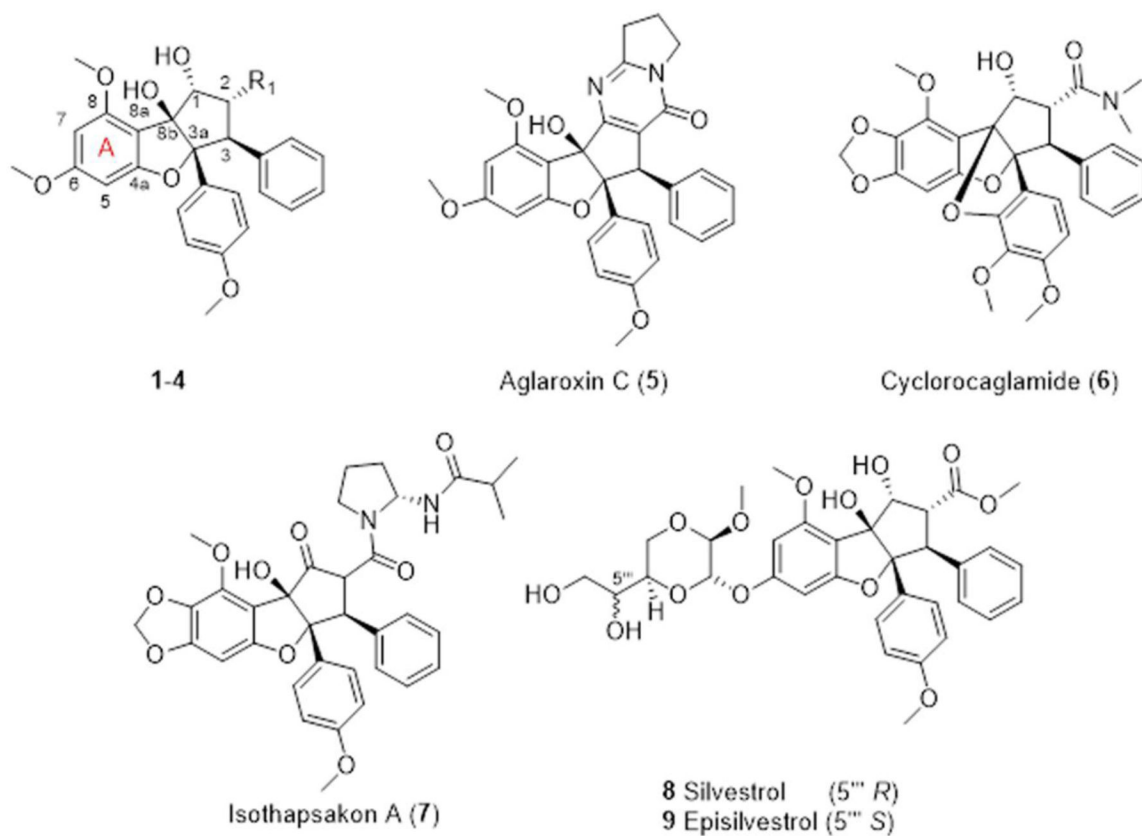
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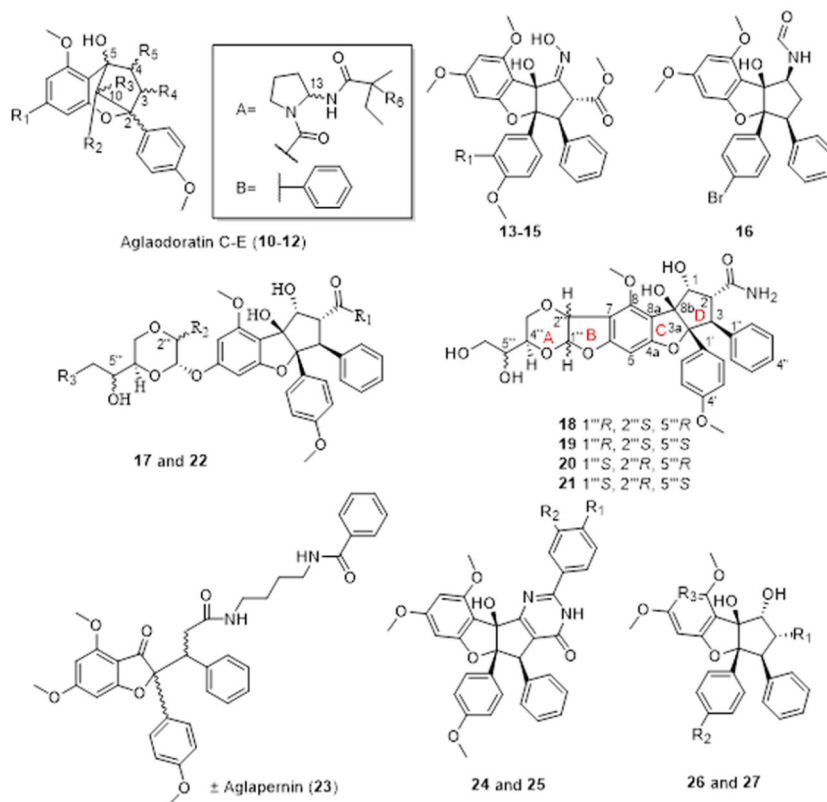
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	R₁
1 Rocaglamide	CONMe ₂
2 Methyl rocaglate	COOMe
3 Didesmethylocaglamide (DDR)	CONH ₂
4 Rocaglaol	H

Fig. 1.
Examples of selected flavaglines (**1-9**) isolated from various *Aglaia* species



		R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
10	Aglaodoratin C (2 <i>S</i> , 3 <i>R</i> , 4 <i>S</i> , 5 <i>S</i> , 13 <i>R</i>)	OMe	R ₂ = R ₃ = O		unit B	unit A	OH
11	Aglaodoratin D (2 <i>S</i> , 3 <i>S</i> , 4 <i>R</i> , 5 <i>S</i> , 10 <i>R</i> , 13 <i>S</i>)	OH	H	OH	unit A	unit B	H
12	Aglaodoratin E (2 <i>R</i> , 3 <i>R</i> , 4 <i>S</i> , 5 <i>R</i> , 10 <i>S</i> , 13 <i>R</i>)	OMe	H	OH	unit A	unit B	OH
13	Rocaglamide AY	H	-	-	-	-	-
14	Aglaodoratin I	OH	-	-	-	-	-
15		OMe	-	-	-	-	-
17	Aglapervirisin A (5''' <i>R</i> , 2''' <i>S</i>)	OMe	OMe	Ac	-	-	-
22	2''' <i>(R/S)</i> (5''' <i>S</i>)	NH ₂	OH	OH	-	-	-
24		Me	H	-	-	-	-
25		H	OMe	-	-	-	-
26	(-)-CR-31-B	CONHOMe	OMe	C	-	-	-
27	eFT-226	CH ₂ NMe ₂	CN	N	-	-	-

Fig. 2. Structures of cytotoxic rocaglates isolated from various *Aglaia* species and of several related synthetic congeners (10-27)

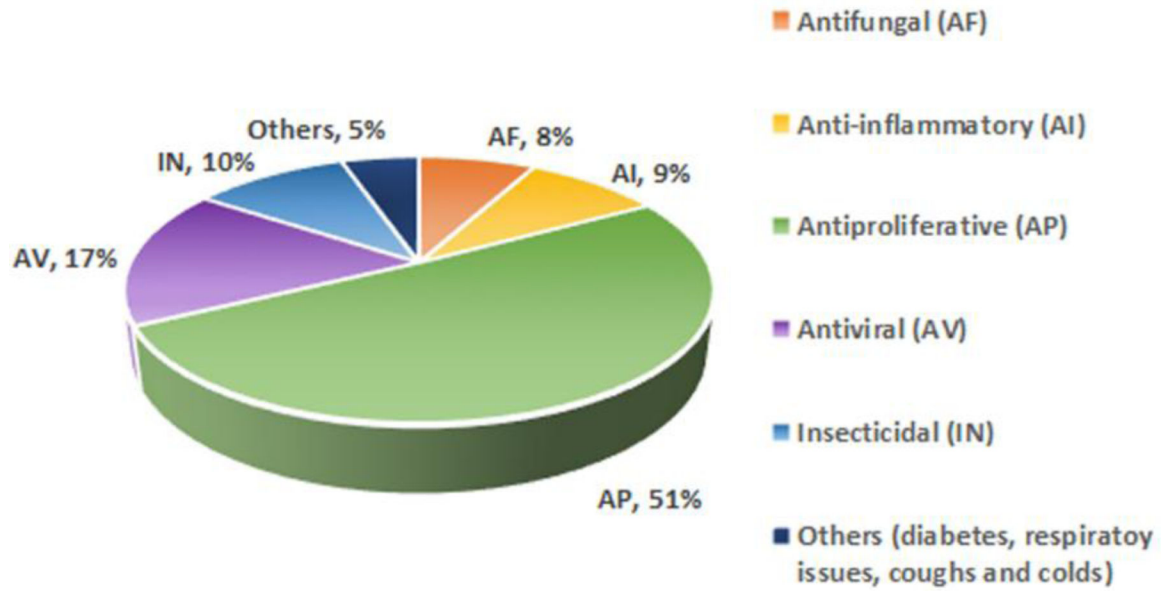


Fig. 3: Graphical representation of publications on *Aglaia* spp. and rocaglate derivatives, with respect to different disease states, 2014–2020 (n = 77, primary research articles).

Table 1:*Aglaia* species collected in Southeast Asia under two NCI-funded research projects

COUNTRY	SPECIES	VOUCHER SPECIMEN
Thailand	<i>Aglaia elliptica</i> Bl.	Nantasan s.n.
Laos	<i>Aglaia</i> cf. <i>macrocarpa</i> King	Soejarto et al. 15399
Laos	<i>Aglaia</i> cf. <i>oligophylla</i>	Soejarto et al. 15396
Laos	<i>Aglaia spectabilis</i> (Miq.) Jain & Bennet	Soejarto et al.15410
Vietnam	<i>Aglaia</i> cf. <i>aquatica</i> (Pierre) Harms	Soejarto et al. 15176
Vietnam	<i>Aglaia perviridis</i> Hiern	Soejarto et al. 14863
Indonesia	<i>Aglaia</i> cf. <i>argentea</i> Bl.	Riswan ML-039
Indonesia	<i>Aglaia edulis</i> (Roxb.) Wall.	Riswan SR-022
Indonesia	<i>Aglaia elliptica</i> Bl.	Riswan ML-033
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan KP-034
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS02
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS17
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS18
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS23
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS24
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS24
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS25
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS26
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS26
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS27
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan SR-IS28
Indonesia	<i>Aglaia foveolata</i> Pannell	Riswan Z-34
Indonesia	<i>Aglaia korthalsii</i> (Miq.) Pellegr.	Kardono SC87
Indonesia	<i>Aglaia leptantha</i> Miq.	Riswan SR-IS01
Indonesia	<i>Aglaia odorata</i> Lour.	Riswan A-12
Indonesia	<i>Aglaia odoratissima</i> Bl.	Riswan SR-072
Indonesia	<i>Aglaia rubiginosa</i> (Hiern) Pannell	Riswan Z-55
Indonesia	<i>Aglaia silvestris</i> Merr.	Riswan SR-J17
Indonesia	<i>Aglaia silvestris</i> Merr.	Riswan SR-068
Indonesia	<i>Aglaia silvestris</i> Merr.	Riswan SR-CJR068
Indonesia	<i>Aglaia teysmanniana</i> (Miq.) Miq.	Riswan SR-J20
Indonesia	<i>Aglaia tomentosa</i> Teijsm. & Binn.	Riswan B-037