Review Article

Genus Miliusa: A Review of Phytochemistry and Pharmacology

Ninh The Son

Institute of Natural Products Chemistry, Vietnam Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam

Correspondence should be addressed to Ninh The Son; yamantson@gmail.com

Received 1 July 2019; Accepted 15 July 2019; Published 14 August 2019

Academic Editor: Armando Zarrelli

Copyright © 2019 Ninh The Son. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Genus Miliusa (family Annonaceae), widely distributed in mainland Asia and Australia to New Guinea, has been employed in both traditional herbal uses and pharmacological medicines. Original research articles related to this genus are now available, but supportive reviews highlighting phytochemical and pharmacological aspects are now insufficient. Objective. This account is an overview of most of the compounds isolated from this genus, along with their pharmacological evaluations.

Conclusion. A vast amount of data showed that genus Miliusa contained various classes of secondary metabolites. Herein, more than two hundred constituents were isolated, comprising alkaloids, geranylated homogentisic acids, flavonoids, lignans, neolignans, terpenoids, acetogenins, styryls, lactones, phenolics, amides, alcohols, and furfural derivatives. Novel miliusanes and bicyclic lactones have been remarkable characteristics of Miliusa plants. Essential oils from these plants were also detected, with a high amount of β-caryophyllene. Numerous in vitro biological researches on, for example, anticancer, antifungal, antimycobacterial, anti-inflammation, and cardiac activity, especially in terms of cytotoxicity, using either isolated compounds or plant extracts, implied that Miliusa phytochemical components now set out to have a key role in pharmacological development. M. smithiae ethyl acetate extract and its flavonoid ayanin (75) inhibited the growth of MCF-7 cell line comparable with positive control ellipicine. (+)-Miliusol (72) stimulated in vivo anticancer experiment against HCT116 xenograft mouse tumor following the p21-dependent induction of cellular senescence mechanism.

1. Introduction

People around the world have been extensively using herbal plants and their products for healthcare objectives. As can be seen, the aromatic medicinal plants have been extensively researched as an important resource of commercial drugs because of their wide traditional uses and pharmacological potencies [1]. Natural products are also recognized to be among the richest resources for new drugs and/or drug leaders due to their high structural diversity as they are not available throughout synthetic pathways [2]. Genus Miliusa (family: Annonaceae) comprises about 60 species and is widely native throughout India and Bhutan to Australia and New Guinea, but mostly found in many Asia countries such as Vietnam, Thailand, and China [3].

More than thirty newly rare secondary metabolites belong to derivatives of geranylated homogentisic acid; in particular, the serial novel miliusanes I-XXXI could be seen as characteristic signals to recognize plants from genus Miliusa.

Phytoconstituents derived from Miliusa plants were subjected to cytotoxic activity, acetylcholinesterase inhibition, activation of cardiac myosin ATPase, anticancer, antifungal, antibacterial, anti-malaria, anti-inflammation, anti-herpes, and antioxidant activity [4–14].

In Southeast Asian traditional medicines, M. balansae species was used for gastropathy and glomerulonephropathy, M. velutina was recommended as tonic and aphrodisiac medicine, or with Thai people, M. thorelii species, also known as “Maa-Dam”, was applied to analgesic treatment [7, 8].

Secondary metabolites from medicinal plants of genus Miliusa are renowned for traditional uses and pharmaceutical potentials. However, there have not been specific reviews to assess the value of this genus, to the best of our knowledge. The current paper deals with most researches over the past 20 years related to Miliusa species and has given a great insight into the botanical description, the correlated chemical isolated compounds in phytochemical aspect, and their role in pharmacological applications. Databases used to search for literature mostly rely on the Plant List, SCI-Finder, Google
2. Botanical Description

(i) Nomenclature: According to a database of the Plant List (www.Theplantlist.org, 2019), the following acceptable names of thirteen *Miliusa* species were listed at a level of high confidence: *M. balansae* Finet & Gagnep., *M. bannaensis* X.L. Hou, *M. brahei* (F. Muell.) Jessup, *M. glochidioides* Hand.-Mazz., *M. horsfieldii* (Bennett) Baill. ex Pierre, *M. indica* Lesch. ex A.DC., *M. macropora* Miq., *M. prolific* (Chun & F.C. How) P.T. Li, *M. sclerocarpa* (A.DC.) Kurz, *M. sinensis* Finet & Gagnep., *M. tenuistipitata* WT. Wang, *M. traceyi* Jessup, and *M. velutina* (A.D.C.) Hook.f. & Thomson [15].

Besides known nineteen Thai species, from morphological point of view, seven new species were found in Thailand: *M. fragrans* Chaowasku & Kessler sp. nov., *M. hirsuta* Chaowasku & Kessler sp. nov., *M. intermedia* Chaowasku & Kessler sp. nov., *M. nakhonsiana* Chaowasku & Kessler sp. nov., *M. sessilis* Chaowasku & Kessler sp. nov., *M. thailandica* Chaowasku & Kessler sp. Nov., and *M. umpanensis* Chaowasku & Kessler sp. nov. [16]. By using DNA-barcoding analysis and the morphological comparisons with the two species *M. punila* Chaowasku and *M. filipes* Ridl., *M. chantaburiana* Damthongdee & Chaowasku was recorded as a new species, growing in Bangko, Thailand [17]. In the same way, an allied member of *M. indica* Leschen, named *M. jainii* Goel at Sharma, sp. nov., was discovered in South Andaman, India, and three new species, *M. cambodgensis* sp. nov., *M. astiana*, and *M. ninhbinhensis* spp. nov., were reported to grow in Cambodia and Vietnam, respectively [3, 18].

(ii) Phylogeny: Genus *Miliusa* belongs to the tribe Miliuseae of the subfamily Malmeoeae of the pantropical Annonaceae [16, 19]. Plants of this genus established a close relationship with two genera, *Hyalostemma* Wall and *Saccopotetum* Benn., and a distinguishing feature between them can be the different number of ovules (*Hyalostemma* only one, *Miliusa* two, and *Saccopotetum* more than two) [19].

(iii) General morphology: The plants exist in shape of shrub or tree (up to ca. 40 m high). The wood appeared yellow when fresh but became darker on exposure; the parenchyma was in fine tangential lines, forming a network with the narrow to moderately broad to broad rays. The mature leaf in *M. horsfieldii*, for instance, indicated elliptic to ovate shape [19]. *Miliusa* species have also been shown to be associated with the following characteristics: equally sized sepal and outer petals both of which are much smaller than the inner petals, a densely hairy torus, miliusioid stamens, i.e. stamens without conspicuously dilated connective tissue covering the thecae, and four part-lamellate ruminations of the endosperm [16].

(iv) Distribution: Genus *Miliusa*, until now, has been reported to consist of about 60 species [17], distributed throughout India and Bhutan to Australia and New Guinea, but mostly found in mainland Asia [19].

3. Phytochemical Investigation

Nowadays, the methods and the processes of the isolation and elucidation of naturally occurring compounds from the medicinal plants have received heavy supports from the modern techniques, such as high performance liquid chromatography (HPLC), gas chromatography-mass spectrum (GC-MS), nuclear magnetic resonance (NMR), ultraviolet-visible (UV-Vis), infrared (IR), optical rotation (OR), and circular dichroism (CD) spectroscopies [1, 20]. We, herein, set out an updated phytochemical account of all isolated metabolites from *Miliusa* species, principally based on chromatographic procedures. Many works have been carried out on the phytochemical investigations of several parts of ten plants, namely, *M. balansae*, *M. CF. banacea*, *M. cuneata*, *M. fragrans*, *M. mollis*, *M. sinensis*, *M. smithiae*, *M. thorelli*, *M. umpanensis*, and *M. velutina* [4, 7, 21–26]. Two hundred twenty secondary metabolites were recorded and presented in Table 1 and Figures 1–9. The names of the isolated compounds have been prepared following the arrangement of alphabetical words. In addition, Table 2 indicated a list of main essential oils from five studied species: *M. baillonii*, *M. brahei*, *M. horsfieldii*, *M. traceyi*, and *M. sinensis* [27–29]. Isolated metabolites of *Miliusa* species were classified into a wide range, including alkaloids, geranylated homogentisic acids, flavonoids, lignans and neolignans, acetogenins, styryls, mono-phenols, terpenoids, amines and amides, alcohols, furans, and other types. The first group of thirty-two compounds 1–32 was referred to as alkaloids [4, 7, 21–26]. Forty-one metabolites from compound 33 to compound 73 could be conveniently classified into the group of homogenistic acid derivatives [7, 13, 14, 30–34]. The structures 74–116 were recognized to be flavonoids [7, 8, 11, 25, 30, 33, 35–38]. Lignans and neolignans were also found in the plants of genus *Miliusa* and were actually described by the state of next compounds 117–144 [7, 9, 10, 24]. Due to the remarkable features, the serial compounds 145–158 were assignable to the group of acetogenin derivatives [5, 32, 38–40]. Ten compounds 159–168 can be seen as lactones [11, 38], and eight constituents 169–176 belonged to styryl derivatives [31, 32, 38, 41]. Terpenoids included the structures 177–185 [11, 25, 37, 42]. The reports of mono-phenols and their glycosides from *Miliusa* species are now available elsewhere, but, herein, they were summed up in a total of thirteen compounds 186–198 [11, 24, 30, 32, 42]. Six amines and amides 199–204 [7, 8, 26], six alcohols 205–210 [11], three aldehyde type furfurals 211–213 [32], and last compounds 214–220 [25, 26, 32, 41] have been identified as the remaining metabolites present in genus *Miliusa*.

3.1. Alkaloids. With natural product substances, alkaloidal compounds were famous long ago. The proportion of alkaloids has been found to deeply depend on the typical parts of the plants and environmental effects. For example, Aniszewski (2007) suggested that a large percentage of alkaloids reached up to 10–25% from the higher plants [1]. *Miliusa* species also provide a rich alkaloidal source. Up to now, over thirty alkaloidal constituents 1–32 were recorded, involved in the previous phytochemical investigations on several plants,
Table 1: Chemical constituents from *Miliusa* species.

| No. | Compounds                                         | Species                      | References          |
|-----|--------------------------------------------------|------------------------------|---------------------|
| 1   | Asimilobine                                       | *M. mollis* twig             | [24]                |
| 2   | Coclaurine                                        | *M. balansae* stem           | [26]                |
| 3   | Dehydroxylophone                                  | *M. cuneata* stem and leaf   | [21]                |
| 4   | 1,9-Dihydroxy-2,11-dimethoxy-4,5-dihydro-7-oxoaporphine | *M. cuneata* stem and leaf   | [21]                |
| 5   | 2,10-Dimethoxy-3,11-dihydroxy-5,6-dihydroprotoberberine | *M. cuneata* stem and leaf   | [21]                |
| 6   | N,O-Dimethylharnovine                             | *M. cuneata* stem and leaf   | [21]                |
| 7   | 10-Hydroxylirodenine                              | *M. CF. banacea* root        | [4]                 |
| 8   | Isocoryline                                       | *M. velutina* stem bark      | [23]                |
| 9   | (+)-Isocoryline α-N-oxide                         | *M. velutina* stem bark      | [22]                |
| 10  | Kinabaline                                        | *M. cuneata* stem and leaf   | [21]                |
| 11  | Lanuginosine                                      | *M. cuneata* stem and leaf   | [21]                |
| 12  | Lirodenine                                        | *M. balansae* stem; *M. cuneata* stem and leaf; *M. mollis* twig, *M. sinensis* leaf and branch; *M. velutina* stem bark | [21, 23–26, 37] |
| 13  | (+)-Liriottupiferine                              | *M. cuneata* stem and leaf   | [21]                |
| 14  | 10-Methoxylirodenine (lauterine)                  | *M. CF. banacea* root        | [4]                 |
| 15  | 1-N-Methylococlaurine                             | *M. balansae* stem           | [26]                |
| 16  | N-Methylcorydaldine                               | *M. cuneata* stem and leaf   | [21]                |
| 17  | N-Methylindcarpine                                | *M. cuneata* stem and leaf   | [21]                |
| 18  | Miliusacunine A                                   | *M. cuneata* leaf            | [7]                 |
| 19  | Miliusacunine B                                   | *M. cuneata* leaf            | [7]                 |
| 20  | Miliusacunine C                                   | *M. cuneata* leaf            | [7]                 |
| 21  | Miliusacunine D                                   | *M. cuneata* leaf            | [7]                 |
| 22  | Miliusacunine E                                   | *M. cuneata* leaf            | [7]                 |
| 23  | Miliusathorine A                                  | *M. thorelii* stem and root  | [8]                 |
| 24  | Miliusathorine B                                  | *M. thorelii* stem and root  | [8]                 |
| 25  | Norcorydine                                       | *M. velutina* stem bark      | [23]                |
| 26  | (-)-Nordicentrine                                 | *M. cuneata* stem and leaf   | [21]                |
| 27  | Norisocorytuberine                                | *M. cuneata* stem and leaf   | [21]                |
| 28  | (-)-Norushinsunine                                | *M. mollis* twig; *M. thorelii* stem and root | [8, 24]          |
| 29  | Pseudocolumbamine                                 | *M. cuneata* stem and leaf   | [21]                |
| 30  | Reticuline                                        | *M. velutina* stem bark      | [23]                |
| 31  | Salutarine                                        | *M. cuneata* stem and leaf   | [21]                |
| 32  | Wilsonirine                                       | *M. cuneata* stem and leaf   | [21]                |
| 33  | Homogentisic acid derivatives                     |                              |                     |
| 34  | Methyl 2-(1’β-geranyl-5’β-hydroxy-2’-oxocyclohex-3’-enyl) acetate | *M. um pangensis* leaf; *M. velutina* fruit | [32, 33]          |
| 35  | Miliusanal                                        | *M. velutina* fruit          | [32]                |
| 36  | Miliusanone A                                     | *M. velutina* fruit          | [32]                |
| 37  | Miliusanone B                                     | *M. velutina* fruit          | [32]                |
| 38  | Miliusanone C                                     | *M. velutina* flower         | [32]                |
Table 1: Continued.

| No | Compounds | Species                          | References               |
|----|-----------|----------------------------------|--------------------------|
| 39 | Miliusanone D | *M. velutina* flower           | [32]                     |
| 40 | (+)-Miliusate | *M. balansae* leaf, branch and stem; *M. sinensis* leaf, twig and flower; *M. umpangensis* leaf | [13, 14, 31, 33, 34] |
| 41 | (+)-Miliusane I | *M. balansae* stem; *M. sinensis* leaf, twig and flower; *M. umpangensis* leaf | [13, 14, 33] |
| 42 | (+)-Miliusane II | *M. balansae* stem; *M. sinensis* leaf, twig and flower | [13, 14] |
| 43 | (+)-Miliusane III | *M. sinensis* leaf, twig and flower | [14] |
| 44 | (+)-Miliusane IV | *M. sinensis* leaf, twig and flower | [14] |
| 45 | (+)-Miliusane V | *M. sinensis* leaf, twig and flower | [14] |
| 46 | (+)-Miliusane VI | *M. sinensis* leaf, twig and flower | [14] |
| 47 | (+)-Miliusane VII | *M. sinensis* leaf, twig and flower | [14] |
| 48 | (+)-Miliusane VIII | *M. sinensis* leaf, twig and flower | [14] |
| 49 | (+)-Miliusane IX | *M. balansae* stem; *M. sinensis* leaf, twig and flower | [13, 14] |
| 50 | (+)-Miliusane X | *M. sinensis* leaf, twig and flower | [14] |
| 51 | (+)-Miliusane XI | *M. sinensis* leaf, twig and flower | [14] |
| 52 | (+)-Miliusane XII | *M. sinensis* leaf, twig and flower | [14] |
| 53 | (+)-Miliusane XIII | *M. sinensis* leaf, twig and flower | [14] |
| 54 | (+)-Miliusane XIV | *M. balansae* stem; *M. Sinensis* leaf, twig and flower | [13, 14] |
| 55 | (+)-Miliusane XV | *M. balansae* stem; *M. Sinensis* leaf, twig and flower | [13, 14] |
| 56 | (+)-Miliusane XVI | *M. sinensis* leaf, twig and flower | [14] |
| 57 | (+)-Miliusane XVII | *M. balansae* stem; *M. sinensis* leaf, twig and flower | [13, 14] |
| 58 | (+)-Miliusane XVIII | *M. sinensis* leaf, twig and flower | [14] |
| 59 | (+)-Miliusane XIX | *M. sinensis* leaf, twig and flower | [14] |
| 60 | (+)-Miliusane XX | *M. sinensis* leaf, twig and flower | [14] |
| 61 | Miliusane XXI | *M. balansae* stem | [13] |
| 62 | Miliusane XXII | *M. balansae* stem | [13] |
| 63 | Miliusane XXIII | *M. balansae* stem | [13] |
| 64 | Miliusane XXIV | *M. balansae* stem | [13] |
| 65 | Miliusane XXV | *M. balansae* stem | [13] |
| 66 | Miliusane XXVI | *M. balansae* stem | [13] |
| 67 | Miliusane XXVII | *M. balansae* stem | [13] |
| 68 | Miliusane XXVIII | *M. balansae* stem | [13] |
| 69 | Miliusane XXIX | *M. balansae* stem | [13] |
| 70 | Miliusane XXX | *M. balansae* stem | [13] |
| 71 | Miliusane XXXI | *M. balansae* stem | [13] |
| 72 | (+)-Miliusol | *M. balansae* leaf, stem and branch; *M. cuneata* leaf, *M. sinensis* leaf, twig and flower; *M. umpangensis* leaf | [7, 13, 14, 24, 30] |
| 73 | Miliusolidea | *M. balansae* leaf and branch | [30] |

**Flavonoids**

**Flavones**

| No | Compounds | Species                          | References               |
|----|-----------|----------------------------------|--------------------------|
| 74 | Artemetin | *M. thorelii* leaf | [8] |
| 75 | Ayanin (5,3'-dihydroxy-3,7,4'-trimethoxyflavone) | *M. smithiae* leaf and twig; *M. umpangensis* leaf | [33, 36] |
| 76 | Chrysosplenol B (chrysoplenetin) | *M. balansae* leaf and branch; *M. cuneata* twig | [7, 35] |
| No | Compounds                             | Species                                  | References               |
|----|---------------------------------------|------------------------------------------|--------------------------|
| 77 | Chrysosplenol C                        | *M. balansae* leaf and branch             | [11, 30, 35]             |
| 78 | Chrysosplenol D                        | *M. umpangensis* leaf                    | [33]                     |
| 79 | 3,5-Dihydroxy-7,3',4'-trimethoxyflavone | *M. sinensis* leaf and branch             | [25, 37]                 |
| 80 | 6,4'-Dihydroxy-3,5,7-trimethoxyflavone | *M. thorelii* stem and root               | [8]                      |
| 81 | Dimethylmikanin                        | *M. thorelii* stem and root               | [8]                      |
| 82 | 3,5,6,7,3',4'-Hexamethoxyflavone       | *M. thorelii*                            | [8]                      |
| 83 | 5-Hydroxy-3,7-dimethoxy-3,4'-methylenedioxyflavone | *M. cuneata* leaf and twig; *M. thorelii* stem, root and leaf | [7, 8]                   |
| 84 | 5-Hydroxy-3,7,4'-trimethoxyflavone     | *M. smithiae* leaf and twig              | [36]                     |
| 85 | 5-Hydroxy-3,6,7,4'-tetramethoxyflavone | *M. thorelii* stem and root               | [8]                      |
| 86 | 4'-Hydroxy-3,5,6,7-tetramethoxyflavone | *M. thorelii* stem and root               | [8]                      |
| 87 | 4'-Hydroxy-3,5,7,3'-tetramethoxyflavone | *M. balansae* leaf and branch             | [33, 35]                 |
| 88 | Ombuine                                | *M. thorelii* stem and root               | [8]                      |
| 89 | 3-O-Methylkaempferol                   | *M. thorelii* stem and root               | [8]                      |
| 90 | Melisimplexin                          | *M. thorelii* stem and root               | [8]                      |
| 91 | Melisimplin                            | *M. thorelii*                            | [8]                      |
| 92 | Miliufavol                             | *M. balansae* leaf and branch             | [35]                     |
| 93 | Miliusathorone                         | *M. thorelii* stem and root               | [8]                      |
| 94 | Ombuine                                | *M. balansae* leaf and branch; *M. umpangensis* leaf | [33, 35]                 |
| 95 | Pachypodol                             | *M. balansae* leaf and branch; *M. thorelii* leaf | [7, 8, 35]              |
| 96 | 3,5,7,3',4'-Pentamethoxyflavone        | *M. thorelii* stem, root and leaf         | [8]                      |
| 97 | Quercetagrin-3,5,7-trimethyl ether     | *M. thorelii* stem and root               | [8]                      |
| 98 | Quercetagrin-3,5,7,3'-tetramethyl ether| *M. thorelii* stem and root               | [8]                      |
| 99 | Quercetin-3-O-methyl ether             | *M. thorelii* stem and root               | [8]                      |
| 100| Quercetin-3,7-dimethyl ether           | *M. thorelii* stem and root               | [8]                      |
| 101| Quercetin-3,5,3'-trimethyl ether       | *M. thorelii* stem and root               | [8]                      |
| 102| Retusin                                | *M. thorelii* stem and root               | [8]                      |
| 103| Rhamnetin                              | *M. velutina*                            | [38]                     |
| 104| Rutin                                  | *M. balansae* leaf; *M. umpangensis* leaf | [11, 33]                 |
| 105| 7,3',4'-Trimethylquercetin             | *M. umpangensis* leaf                    | [33]                     |
| 106| 2',6'-Dihydroxy-4'-Methoxydihydrochalcon | *M. balansae* leaf and branch             | [31]                     |
| 107| 4',6'-Dihydroxy-2',3',4'-trimethoxydihydrochalcon | *M. sinensis* leaf and branch             | [37]                     |
| 108| Dihydropashanone                       | *M. balansae* leaf and branch; *M. sinensis* leaf and branch | [25, 31, 37]             |
| 109| Pashanone                              | *M. sinensis* leaf and branch             | [6, 25, 37]              |
| 110| 5-Hydroxy-6,7-dimethoxyflavanone (onysilin) | *M. balansae* leaf and branch; *M. sinensis* leaf and branch | [6, 25, 31, 37] |
| 111| 5-Hydroxy-7,8-dimethoxyflavanone       | *M. balansae* leaf and branch             | [25, 31, 37]             |
| 112| 5-Hydroxy-7-methoxyflavanone           | *M. balansae* leaf and branch             | [25, 31, 37]             |
| 113| 5-Hydroxy-7,4'-methoxyflavanone        | *M. balansae* leaf and branch             | [25, 31, 37]             |
| 114| 7-O-Methyleryiodictyol                 | *M. velutina*                            | [38]                     |
| No | Compounds | Species | References |
|----|-----------|---------|------------|
| 115 | Sakuranetin | *M. velutina* leaf | [38] |
| 116 | (-)-Epicatechin | *M. balansae* leaf; *M. fragrans* leaf and stem; *M. mollis* leaf | [9, 11, 24] |

### Lignans and neolignans

#### Lignans

| No | Compounds | Species | References |
|----|-----------|---------|------------|
| 117 | (+)-3-Hydroxyveraguensin | *M. fragrans* stem | [9] |
| 118 | (7S,8S,9R,10S,11S,12R)-7,8,10-trihydroxy-11-(4-hydroxy-3,5-dimethoxyphenyl)heptadeca-10,11-diene-4,11-diol | *M. fragrans* stem and leaf | [9] |
| 119 | (+)-Syringaresinol | *M. cuneata* leaf | [7] |
| 120 | (7S,8S,9R)-7,8,9-trihydroxy-10-(3,4-dimethoxyphenyl)heptadeca-1,10-diene-4,11-diol | *M. fragrans* stem | [9] |

#### Neolignans

| No | Compounds | Species | References |
|----|-----------|---------|------------|
| 121 | 2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl)propane | *M. mollis* leaf | [9] |
| 122 | Conocarpan | *M. mollis* twig | [24] |
| 123 | Decurrenal | *M. mollis* leaf | [10] |
| 124 | [(7S,8R)-4',8'-dimethoxy-3,5',6',7',8',9'-hexahydroxytridec-10'-ene]-4-O-Demethyleusiderin C | *M. fragrans* leaf and stem | [9] |
| 125 | [(7S,8R)-4',8'-dimethoxy-3,5',6',7',8',9'-hexahydroxytridec-10'-ene]-4-O-Demethyleusiderin C | *M. fragrans* leaf and stem | [9] |
| 126 | (2R,3R)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-methyl-5-(1(E))-propenylbenzofuran | *M. mollis* twig | [24] |
| 127 | (2S,3S)-2,3-Dihydro-2-(4-methoxyphenyl)-3-methyl-5-[1(E)-propenyl]benzofuran | *M. mollis* twig | [24] |
| 128 | (+)-Eusiderin A | *M. fragrans* stem | [9] |
| 129 | Eusiderin C | *M. fragrans* stem | [9] |
| 130 | Eusiderin D | *M. fragrans* stem and leaf | [9] |
| 131 | Licarin A | *M. fragrans* leaf | [9] |
| 132 | (7S,8S)-three-4'-4-Methoxyneolignan 7-Methoxymiliumollin [(2R,3R)-5-allyl-2,3-dihydro-2-(4-hydroxyphenyl)-7-methoxy-3-methylbenzofuran] | *M. mollis* twig | [24] |
| 133 | 3'-Methoxymiliumollin [(2R,3R)-5-allyl-2,3-dihydro-2-(4-hydroxyphenyl)-3-methylbenzofuran] | *M. mollis* leaf | [10] |
| 134 | [(2R,3R)-5-allyl-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-methylbenzofuran] | *M. mollis* leaf | [10] |
| 135 | (−)-O-Methylmiliusfragrin [(7R,8R)-Δ8'-3,4,5,10'-tetramethoxy-7-O,3',8-O,4'-neolignan] | *M. fragrans* stem | [9] |
| 136 | 4'-O-Methylmiliusfragrin [(2S,3S)-5-allyl-2,3-dihydro-2-(4-hydroxyphenyl)-3-methylbenzofuran] | *M. mollis* leaf | [10] |
| 137 | (−)-Miliusfragrans B [(Δ8'-9'-hydroxy-3,4,5,10'-tetramethoxy-8-O,4'-neolignan] | *M. fragrans* leaf | [9] |
| 138 | (−)-Miliusfragrans B [(Δ8'-9'-hydroxy-3,4,5,10'-tetramethoxy-8-O,4'-neolignan] | *M. fragrans* leaf | [9] |
| 139 | (−)-Miliusfragrans [(7R,8R)-Δ8'-4-hydroxy-3,5'-dimethoxy-7-O,3',8-O,4'-neolignan] Miliumollin [(2R,3R)-5-allyl-2,3-dihydro-2-(4-hydroxyphenyl)-3-methylbenzofuran] | *M. fragrans* leaf and stem | [9] |
| 140 | M. mollis leaf | *M. mollis* leaf | [10] |
| No  | Compounds                                                                 | Species                | References |
|-----|---------------------------------------------------------------------------|------------------------|------------|
| 141 | Miliumollinone [(2R,3R)-2,3-dihydro-2-(4-hydroxyphenyl)-3-methyl-5-(2-oxopropyl)-benzofuran] | M. mollis leaf        | [10]       |
| 142 | Miliusanollin [(7R,8R)-three-Δ^8^-7-acetoxy-4-methoxy-8-O-4'-neolignan] (7S,8R)-7-hydroxy-3,4,3'-trimethoxy-Δ^1,3,5,1'3',5',8'-8.0'.4'-neolignan | M. mollis leaf        | [10]       |
| 143 | Virolongin B                                                               | M. fragrans leaf      | [9]        |
| 144 | Acetogenins                                                                |                        |            |
| 145 | Acetogenins A                                                              | M. velutina stem bark  | [5]        |
| 146 | Acetogenins B                                                              | M. velutina stem bark  | [5]        |
| 147 | Cananginone A                                                              | M. velutina stem bark and flower | [32, 40] |
| 148 | Cananginone B                                                              | M. velutina stem bark  | [40]       |
| 149 | Cananginone C                                                              | M. velutina stem bark  | [40]       |
| 150 | Cananginone D                                                              | M. velutina stem bark  | [40]       |
| 151 | Cananginone E                                                              | M. velutina stem bark  | [40]       |
| 152 | Cananginone F                                                              | M. velutina stem bark  | [40]       |
| 153 | Cananginone G                                                              | M. velutina stem bark  | [40]       |
| 154 | Cananginone H                                                              | M. velutina stem bark, leaf and flower | [32, 38, 40] |
| 155 | Cananginone I                                                              | M. velutina stem bark  | [40]       |
| 156 | Miliusolide \(^a\)                                                          | M. velutina stem bark  | [39]       |
| 157 | Miliusolide dihydro derivative                                            | M. velutina stem bark  | [39]       |
| 158 | Goniothalamusin                                                            | M. velutina stem bark  | [5]        |
| 159 | Curcolide                                                                  | M. balansae leaf       | [11]       |
| 160 | Serralactone                                                               | M. balansae leaf       | [11]       |
| 161 | Velutinone A                                                               | M. velutina leaf       | [38]       |
| 162 | Velutinone B                                                               | M. velutina leaf       | [38]       |
| 163 | Velutinone C                                                               | M. velutina leaf       | [38]       |
| 164 | Velutinone D                                                               | M. velutina leaf       | [38]       |
| 165 | Velutinone E                                                               | M. velutina leaf       | [38]       |
| 166 | Velutinone F                                                               | M. velutina leaf       | [38]       |
| 167 | Velutinone G                                                               | M. velutina leaf       | [38]       |
| 168 | Velutinone H                                                               | M. velutina leaf       | [38]       |
| 169 | 3,4-Dimethoxy-6-styryl-pyran-2-one                                        | M. balansae leaf and branch | [31]       |
| 170 | (2E,5E)-2-Methoxy-4-oxo-6-phenyl-hexa-2,5-dienoic acid methyl ester        | M. balansae leaf and branch | [31]       |
| 171 | Yangonin                                                                   | M. velutina leaf, fruit and flower | [32, 38] |
| 172 | Miliubisstyryl A                                                           | M. balansae leaf and branch | [41]       |
| 173 | Miliubisstyryl B                                                           | M. balansae leaf and branch | [41]       |
| 174 | Velutinindimer A                                                           | M. velutina leaf, fruit and flower | [32, 38] |
| 175 | Velutinindimer B                                                           | M. velutina leaf, fruit and flower | [32, 38] |
| 176 | Velutinindimer C                                                           | M. velutina leaf       | [38]       |
| 177 | Alangionoside B                                                            | M. balansae stem       | [42]       |

**Table 1: Continued.**
| No  | Compounds                     | Species          | References |
|-----|-------------------------------|------------------|------------|
| 178 | Ampelopsisionoside            | M. balansae leaf | [11]       |
| 179 | Milbaside A                   | M. balansae leaf | [11]       |
| 180 | Milbaside B                   | M. balansae leaf | [11]       |
| 181 | Milbaside C                   | M. balansae leaf | [11]       |
| 182 | Milbasoside C                 | M. balansae stem | [42]       |
| 183 | Myrsininoside A               | M. balansae leaf | [11]       |
| 184 | Myrsininoside D               | M. balansae leaf | [11]       |
| 185 | 24-Methylencycloartane-3β,21-diol | M. sinensis leaf and branch | [25, 37] |
|     | **Triterpenoid**              |                  |            |
| 186 | **Mono-phenols and mono-phenol glycosides** |          |            |
| 187 | bis(2-Hydroxyphenyl)methyl ether | M. balansae leaf and branch | [30]       |
| 188 | Cuchiloside                   | M. balansae stem | [42]       |
| 189 | 4-Hydroxybenzonitrile         | M. velutina fruit | [32]       |
| 190 | 4-Hydroxybenzaldehyde         | M. velutina fruit | [32]       |
| 191 | Icariside D2                  | M. mollis twig   | [24]       |
| 192 | Isovanillin                   | M. velutina fruit | [32]       |
| 193 | Milbasoside A                 | M. balansae stem | [42]       |
| 194 | Milbasoside B                 | M. balansae stem | [42]       |
| 195 | Osmanthuside H                | M. balansae stem | [42]       |
| 196 | 1-(α-L-Rhamnosyl-(1→6)-β-D-glucopyranosyloxy)-3,4,5-trimethoxybenzene | M. balansae stem | [42]       |
| 197 | 3,4,5-Trimethoxyphenol-β-D-glucopyranoside | M. balansae stem | [42]       |
| 198 | Tyrosol-1-O-β-xylopyranosyloxy-6-O-β-glucopyranoside | M. mollis twig | [24]       |
|     | **Amines and amides**         |                  |            |
| 199 | Adenine riboside              | M. balansae stem | [26]       |
| 200 | Allantoin                     | M. balansae stem | [26]       |
| 201 | N-trans-Caffeoyltyramine      | M. cuneata twig; M. thorelii stem and root | [7, 8]     |
| 202 | N-trans-Coumarooyltyramine    | M. cuneata twig | [7]        |
| 203 | N-trans-Feruloyltyramine      | M. cuneata twig; M. thorelii stem and root | [7, 8]     |
| 204 | Uridine                       | M. balansae stem | [26]       |
|     | **Alcohols**                  |                  |            |
| 205 | β-D-Glucopyranoside (Z)-3-hexenol | M. balansae leaf | [11]       |
| 206 | erythro-Guaiaeclyglycerol     | M. balansae leaf | [11]       |
| 207 | threo-Guaiaeclyglycerol       | M. balansae leaf | [11]       |
| 208 | (L)-Guaiaecyl glycerol        | M. balansae leaf | [11]       |
| 209 | 2′-O-β-D-glucopyranoside      | M. balansae leaf | [11]       |
| 210 | erythro-1-C-Syringyglycerol   | M. balansae leaf | [11]       |
| 211 | threo-1-C-Syringyglycerol     | M. balansae leaf | [11]       |
|     | **Furfurals**                 |                  |            |
| 211 | 5-Acetylxylohydrofurfural     | M. velutina fruit | [32]       |
| 212 | 5-Hydroxyhydrofurfural        | M. velutina fruit | [32]       |
| 213 | 5-Methoxyfurfural             | M. velutina fruit | [32]       |
|     | **Others**                    |                  |            |
| 214 | D-Glucose                     | M. balansae stem | [26]       |
M. balansae, M. CF. banacea, M. mollis, M. sinensis, M. thorelii, and M. velutina, but mostly found in M. cuneata (Figure 1) [4, 7, 21–26, 37]. Among them, eleven constituents, namely, compounds 4-5, 7, 9, and 18-24, were new in nature. Liriiodenine (12) was likely to be familiar with plants from genus Miliusa and widely distributed in M. balansae stem, M. cuneata stem and leaf, M. mollis twig, M. sinensis leaf and branch, and M. velutina stem bark [21, 23–26, 37]. With the exception of new compounds and two known others, 12 and 28, it was remarked that the remaining compounds were isolated from this genus for the first time. Miliusa alkaloids can be found in formulating a variety of main skeletons, such as aporphine and oxo-aporphine backbones in respective asimilobine (I) and 10-hydroxyliriiodenine (7), tetrahydroisoquinoline and quinolone in respective coclaurine (2) and N-methylcorydalidine (16), azafuorenone in kinabaline (10), dihydropseudoberberine and oxo-protoberberine in respective 2,10-dimethoxy-3,11-dihydroxy-5,6-dihydroprotoberberine (5) and miliusacunine A (18), benzylisoquinoline in reticuline (30), or morphinan in salutarine (31).

Taking the newly isolated alkaloids into consideration, two new oxo-aporphine and dihydroprotoberberine alkaloids 4-5, in addition to thirteen known others (Table 1), were obtained from 95% ethanol extract of air-dried and powdered stem and leaf of M. cuneata [21]. One of the immensely value aspects of 2,10-dimethoxy-3,11-dihydroxy-5,6-dihydroprotoberberine (5) is that this compound possessed the positive and negative charges in nitrogen and oxygen atoms, respectively [21]. Khan and Kumar (2015) suggested that alkaloids with bipolar charges had a tendency to bind to the serum proteins better than that of neutral compounds [43].

Following the outcomes in the isolation and NMR-structural elucidation, 10-methoxyliroidioline (14) was a known alkaloid, but its 10-hydroxylated derivative 7 was determined to be a new oxo-aporphine alkaloid in nature; both of these two compounds were precipitated out of the MeCOEt extract (2.8 g) of M. CF. banacea species [4]. Likewise, isocorydine (8), especially its new unusual derivative (+)-isocorydine α-N-oxide (9), has successfully been separated from extracts of M. velutina stem bark [22, 23].

An additional significance in phytochemical works related to plants is that the leaf of M. cuneata species is likely to be a rich source of oxo-protoberberine alkaloids. In 2005, five new alkaloids of type oxo-protoberberine were isolated from the acetone extract of M. cuneata leaf, trivially named miliusacunines A-E (18-22) [7].

Finally, three alkaloids, consisting of two new dihydro-oxo-protoberberine derivatives miliusathornines A-B (23-24) and known one (−)-norushinsunine (28), have been purified from the combined extract between stem and root of M. thorelii species [8].

3.2. Geranylated Homogentisic Acid Derivatives. Phenolic acids of type homogentisic acids are usually detected in both terrestrial plants and bacterial pathogenic strains [44, 45]. Homogentisic acids indicated the significant antioxidant and anti-inflammatory capacities, but the excess accumulation of these can cause “alkapton” symptom in the human body [45, 46].

Considerable attention should be paid to the novel class of geranylated homogentisic acid derivatives from plants of genus Miliusa. Among the total forty-one isolated compounds 33-73, secondary metabolites 40-73 were novel and relatively rare compounds in nature while a number of isolates 35-39 were new in literature.

General features were highlighted in the chemical structures 33-34 and 36-72; that is, carbonylation and geranylation often occurred at carbons C-2 (or C-2‘) and C-1 (or C-1‘), respectively (Figure 2). Furthermore, double bonds might be located at carbons C-3 and C-4 (or C-3′ and C-4′); hydroxylation, methoxylation, or acetoxylation was normally observed at carbon C-5 (or C-5′).

Of isolated compounds 40-72, most of these unique structures might possibly be formed by a rare C-18 skeleton, containing a characteristic γ-lactone spiro-ring system. Five-member γ-lactone ring were geranylated in the structures 40-57, 61-67, and 72, but were found to be opened in the structures 58-60 and 68-71. Two isolated compounds 59-60 also contained a tetrahydrofuran ring. Additionally, the combination of NOE effect observations, Mosher reactions, and X-ray measurements allowed for determining the absolute configuration, in which 1R,5S,1′R-form and 1S-orientation were suitable for the group of compounds 40-72 [14]. 

13C-NMR provided the evidence of chemical shifts δC, thereby showing that, at carbons C-1, C-5, and C-1’ of compounds containing spiro-ring system, δC reached ca. 52.0-56.0 ppm, ca. 63.0-68.0 ppm, and ca. 26 ppm, respectively.

Table 1: Continued.

| No  | Compounds            | Species                                  | References |
|-----|----------------------|------------------------------------------|------------|
| 215 | Octacosanoic acid    | M. balansae leaf and branch              | [41]       |
| 216 | β-Sitosterol         | M. balansae stem; M. velutina fruit      | [26, 32]   |
| 217 | β-Sitosterol glucoside| M. balansae stem; M. sinensis leaf and branch | [25, 26] |
| 218 | Sodium benzoate      | M. balansae leaf and branch              | [30]       |
| 219 | Stigmasterol         | M. sinensis leaf and branch; M. velutina fruit and flower | [25, 32] |
| 220 | Sucrose              | M. balansae stem                         | [26]       |
As part of an interdependent work, more recently, Promgool et al. (2019) reported that chromatographic separation of extracts of *M. velutina* fruit and flower has resulted in isolating and elucidating five new rare geranylated homogentisic acid derivatives, miliusanal (35) and miliusanones A-D (36-39), in addition to known ones, methyl 2-(1’β-geranyl-5’β-hydroxy-2’-oxocyclohex-3’-enyl) acetate (33) and 2-(1’β-geranyl-5’β-hydroxy-2’-oxocyclohex-3’-enyl) acetic acid (34) [32]. New compound 35 indicated the property of a phenolic aldehyde with CHO (δ_C 196.1 ppm in solvent CDCl₃), whereas new compounds 38-39 were significantly made of 6’-hydroxylated groups (δ_C 75.6-77.4 ppm in solvent CDCl₃ + CD₃OD).

Novel (+)-miliusate (40) was one of the interesting constituents of Vietnamese plant *M. balansae* [31]. After that, it was reported appearing in two other species: *M. sinensis* leaf, twig and flower, and *M. umpangensis* leaf [14, 19, 33, 34]. So far, the methanol-water extract (95:5, v/v) of

**Figure 1**: Alkaloids from *Miliusa* species.
Figure 2: Continued.
Vietnamese plant *M. balansae* leaf and branch has shown to comprise one novel compound, (+)-miliusol (72), and one new natural product, miliusolide (73) [30]. In NOE interactions H-3a to H-5 and H-7a were key evidence to determine these three protons with oriented cis-shape and the absolute configuration was established as 3aS,5S,7aR in compound 73.

Novel geranylated homogentisic acids derived *Miliusa* plants were more commonly referred to by their trivial name. By using Table 1 and Figure 2, we continue to make comments relating to a serial number of (+)-miliusanes I-XXXI (41-71). Secondary metabolites 41-60 were separated from dichloromethane extract of the other Vietnamese plant *M. sinensis* leaf, twig, and flower, whereas the remaining members 61-71, once again, derived from *M. balansae* species [13, 14]. As shown in Figure 2, the plausible biogenetic pathway explained why these compounds were classified as geranylated homogentisic acids, in which the first step involved the combination between precursor homogentisic acid and geranyl unit of geranyl diphosphate (geranyl PP). Obviously, the methylation of intermediate product A produced compound 53 while lactone ring-cyclization and dehydrate applied to A would give 72; compound 53 was then joined to epoxide ring-cyclization reaction and dehydrated to form 59 [14].

3.3. Flavonoids. Now we do take a point of crucial information in mentioning another class of *Miliusa* metabolites. Phytochemical investigations on *Miliusa* species also proved the existence of flavonoids. Flavonoids were detected in leaf, twig, branch, stem, or root of nine plants: *M. balansae, M. cuneata, M. fragrans, M. mollis, M. sinensis, M. smithiae, M. thorelii, M. umpangensis*, and *M. velutina*, to date (Table 2).

Herein, we draw a list of forty-three isolated compounds 74-116 from *Miliusa* species. Chemical index also exhibited that *Miliusa* flavonoids can be divided into several main groups: flavonols 74-105, chalcones 106-109, flavanones 110-115, and flavan 116 (Table 1 and Figure 3) [7, 8, 11, 25, 30, 33, 35–37]. More than thirty flavonols were found but flavones and isoflavones were absent, to the best of our knowledge. Likewise, flavanones and isoflavanones have not been recorded yet.

The most important information to be gained from structural features is that isolated flavonoids derived from *Miliusa* species were generated as mono-flavonoid derivatives. The phenomenon of methoxylation occurred at carbon C-3 of most isolated flavonols. Normally, flavonols and flavanones were associated with substituents at carbons C-5, C-6, C-7, C-8, C-3’, and C-4’ by hydroxy and methoxy groups.

Despite the fact that the known flavonoids 74, 77-82, 84-91, 96-99, 101-103, 105-107, 109, and 114-115 are abundant in the plant kingdom, these compounds were reported from *Miliusa* species for the first time. Rutin (104) was recognized to be only flavonol glycoside isolated from plants of genus...
Table 2: Essential oils from presentative *Miliusa* species.

| Species       | Collections        | Part Uses                  | Main constituents                                                                 | References |
|---------------|---------------------|----------------------------|-----------------------------------------------------------------------------------|------------|
| *M. baillonii* | Quang Binh-Vietnam  | Fresh leaf                 | Naphthalene (1.0%), bicycloelemene (1.1%), germacrone B (1.2%), germacrone D (1.2%), δ-cadinene (1.4%), isosigmaflorene (1.2%), spathulenol (1.4%), α-terpinolene (1.5 %), elemol (1.7%), linalool (2.7%), β-elemene (3.5%), τ-murolol (3.8%), α-humulene (6.2%), β-caryophyllene (10.6%), and Z-citral (41.2%) | [28]       |
| *M. sinensis*  | Nghean-Vietnam      | Dried leaf                 | (E)-β-Ocimene (2.4%), aromadendrene (6.6%), β-elemene (71%), α-humulene (79%) and β-caryophyllene (19.5%) | [29]       |
| *M. brahei*    | 16°31’S, 145°28’E   | Leaf                      | Cubeban-11-ol (1.0%), caryophyllene oxide (1.1%), α-copaene (1.2%), α-selinene (1.2%), viridiflorene (1.2%), δ-cadinene (1.8%), viridiflorol (1.8%), β-selinene (2.2%), geranial (2.3%), (Z)-β-ocimene (2.6%), aromadendrene (3.0%), globulol (3.3%), α-terpinol (3.5%), spathulenol (3.6%), germacrone D (5.3%), linalool (7.4%), α-humulene (11.3%), β-caryophyllene (12.8%) and bicyclogermacrene (12.9%) | [27]       |
| *M. horsfieldii*| 13°48’S, 143°28’E   | Leaf                      | Geranial (1.0%), globulol (1.2%), cubeban-11-ol (1.3%), bicycloelemene (1.8%), α-cadinol (1.9%), allo-aromadendrene (1.9%), viridiflorene (2.5%), bicyclogermacrene (2.5%), α-selinene (2.6%), β-selinene (2.8%), δ-cadinene (3.0%), α-humulene (3.4%), linalool (3.8%), α-copaene (7.5%), caryophyllene oxide (12.5%) and β-caryophyllene (20.2%) | [27]       |
| *M. traceyi*   | 14°00’S, 143°19’E   | Leaf                      | δ-Cadinene (1.8%), α-humulene (2.4%), spathulenol (2.9%), limonene (3.0%), bicyclogermacrene (3.8%), germacrone D (4.9%), β-caryophyllene (13.5%), β-pinene (18.6%) and α-pinene (18.7%) | [27]       |

*Miliusa*. In the meantime, (−)-epicatechin ([116]) was also a unique flavan to be found.

*M. thorelii* species seemed to be a rich supply of flavonols. Bioguided assay and fractionation of extracts of leaf, stem, and root afforded one new natural product, *miliusathorone* ([86]), and root afforded one new natural product, *miliusathorone* ([87]). In the meantime, (−)-epicatechin ([116]), in addition to nineteen known ones, 74, 80–83, 85–86, 88–91, and 95–102 [8]. New metabolite 92 had the characteristic remark with chemical shifts of -O-CH₃, δ-C₆H₆, δ-C = 101.8. Interestingly, new metabolite named *miliufavol* (92) was derived from methanol-water (95:5, v/v) extract of air-dried ground *M. balansae* leaf and branch [35], in which this compound was an uncommon flavonol by combining of pachypodol (95) and benzyl unit at carbon C-8.

Four chalcone derivatives, 2',6'-dihydroxy-4'-methoxy-dihydrochalcone (106), 4',6'-dihydroxy-2',3',4'-trimethoxy-dihydrochalcone (107), dihydroshalanone (108), and pashanone (109), were significant constituents of the two Vietnamese plants *M. balansae* and *M. sinensis* [25, 31, 37]. In contrast to 109, three compounds 106–108 belong to dihydrochalcone, and compound 107 was a new isolated compound in literature. Isolated flavanones 110–113 were also considered as main components of Vietnamese *M. balansae* and *M. sinensis*, but two compounds, final derivatives 7-O-methyleriodictyol ([114]) and sakuranetin ([115]), were only detected in *M. velutina* leaf up to now [38].

3.4. Lignans and Neolignans. We continuously provide the next phytochemical profiles of the other class of isolated compounds. Starting with the deepest aim to find biologically active molecules from genus *Miliusa*, four lignans 117–120 and twenty-four neolignans 121–144 have also been isolated (Table 1 and Figure 4). In addition, these phytochemicals from genus *Miliusa* originated from three parts, leaf, stem, and twig, of two main species, *M. fragrans* and *M. mollis*, but occasionally found in *M. cuneata* species [8–10, 24].

It is possible to set up a clear arrangement for backbones of either lignans or neolignans. *Miliusa* lignans were able to form up to two main skeletons, tetrahydrofuran lignan (compounds 117–118 and 120) and 7',9'-diepoxylignan (compound 119). In the case of neolignans, three main scaffolds can be found, namely, 8.O.4'-neolignan (compounds 121, 132, 137–138, and 142–144), 7.O.3',8.O.4'-neolignan (124–125, 128–130, 135, and 139), and dihydrobenzofuran skeleton (compounds 122–123, 126–127, 131, 133–134, 136, and 140–141). Two skeletons of 8.O.4'-neolignan and 7.O.3',8.O.4'-neolignan were only represented in the two Thai species
Table 3: Cytotoxic results of Miliusa components.

| No | Inhibitory concentrations (cell lines)                                                                 | References |
|----|-------------------------------------------------------------------------------------------------------|------------|
| 12 | IC₅₀ 2.89 µg/mL (MCF-7), IC₅₀ 6.66 µg/mL (LU), IC₅₀ 5.23 µg/mL (Hep-G2) and IC₅₀ 2.30 µg/mL (KB)      | [37]       |
| 18-22 | Inactive (KB and Vero)                                                                                  | [7]        |
| 33 | IC₅₀ 26.5 µg/mL (KB), IC₅₀ 32.7 µg/mL (MCF-7), IC₅₀ 5.8 µg/mL (NCI-H187) and IC₅₀ 6.3 µg/mL (Vero)   | [32]       |
| 34 | IC₅₀ 11.8 µg/mL (KB), IC₅₀ > 50.0 µg/mL (MCF-7), IC₅₀ 6.1 µg/mL (NCI-H187) and IC₅₀ 17.7 µg/mL (Vero) | [32]       |
| 35 | IC₅₀ 9.3 µg/mL (KB), IC₅₀ 3.6 µg/mL (MCF-7), IC₅₀ 40.4 µg/mL (NCI-H187) and IC₅₀ 39.1 µg/mL (Vero)  | [32]       |
| 36 | IC₅₀ 11.9 µg/mL (KB), IC₅₀ 23.2 µg/mL (MCF-7), IC₅₀ 6.1 µg/mL (NCI-H187) and IC₅₀ 16.1 µg/mL (Vero) | [32]       |
| 37 | IC₅₀ 17.9 µg/mL (KB), IC₅₀ 26.4 µg/mL (MCF-7), IC₅₀ 6.2 µg/mL (NCI-H187) and IC₅₀ 5.8 µg/mL (Vero)  | [32]       |
| 38 | IC₅₀ > 50.0 µg/mL (KB, MCF-2, NCI-H187, Vero)                                                         | [32]       |
| 39 | IC₅₀ > 50.0 µg/mL (KB, MCF-7, NCI-H187, Vero)                                                         | [32]       |
| 40 | IC₅₀ 5.18 µg/mL (KB), IC₅₀ 2.02 µg/mL (LuL), IC₅₀ 1.56 µg/mL (Col2), IC₅₀ 3.18 µg/mL (LNCaP), IC₅₀ 3.58 µg/mL (MCF-7), IC₅₀ 2.89 µg/mL (HUVEC), IC₅₀ 0.32 µg/mL (HL60), IC₅₀ 2.70 ± 0.09 µM (HCT116), IC₅₀ 1.67 ± 0.11 µM (A375) and IC₅₀ 6.97 ± 0.16 µM (A549) | [13,14] |
| 41 | IC₅₀ 1.40 µg/mL (KB), IC₅₀ 2.86 µg/mL (LuL), IC₅₀ 2.92 µg/mL (Col2), IC₅₀ 5.06 µg/mL (LNCaP), IC₅₀ 2.23 µg/mL (MCF-7), IC₅₀ 1.79 µg/mL (HUVEC), IC₅₀ 0.45 µg/mL (HL60), IC₅₀ 3.50 ± 0.02 µM (HCT116), IC₅₀ 3.70 ± 0.11 µM (A375) and IC₅₀ 4.36 ± 0.40 µM (A549) | [13,14] |
| 42 | IC₅₀ 5.45 µg/mL (KB), IC₅₀ 5.80 µg/mL (LuL), IC₅₀ 9.40 µg/mL (Col2), IC₅₀ 19.64 µg/mL (LNCaP), IC₅₀ 21.34 µg/mL (MCF-7), IC₅₀ 6.55 µg/mL (HUVEC), IC₅₀ 1.73 µg/mL (HL60), IC₅₀ 172 ± 1.86 µM (HCT116), IC₅₀ 9.86 ± 0.19 µM (A375) and IC₅₀ 18.4 ± 0.35 µM (A549) | [13,14] |
| 43 | IC₅₀ 1.18 µg/mL (KB), IC₅₀ 4.84 µg/mL (LuL), IC₅₀ 4.29 µg/mL (Col2), IC₅₀ 5.06 µg/mL (LNCaP), IC₅₀ 2.61 µg/mL (MCF-7) and IC₅₀ 0.56 µg/mL (HL60) | [14]      |
| 44 | IC₅₀ 3.217 µg/mL (KB), IC₅₀ 60.43 µg/mL (LuL), IC₅₀ 38.45 µg/mL (Col2), IC₅₀ > 62.0 µg/mL (LNCaP), IC₅₀ 15.78 µg/mL (MCF-7) and IC₅₀ 18.66 µg/mL (HL60) | [14]      |
| 45 | IC₅₀ > 55.0 µg/mL (KB, LuL, Col2, LNCaP and MCP-7) and IC₅₀ 52.29 µg/mL (HL60) | [14]      |
| 46 | IC₅₀ 3.97 µg/mL (KB), IC₅₀ 6.61 µg/mL (LuL), IC₅₀ 4.23 µg/mL (Col2), IC₅₀ 5.29 µg/mL (LNCaP) and IC₅₀ 4.76 µg/mL (MCF-7) | [14]      |
| 47 | IC₅₀ 5.82 µg/mL (KB), IC₅₀ 6.16 µg/mL (LuL), IC₅₀ 3.70 µg/mL (Col2), IC₅₀ 5.82 µg/mL (LNCaP) and IC₅₀ 6.08 µg/mL (MCF-7) | [14]      |
| 48 | IC₅₀ 47.35 µg/mL (KB), IC₅₀ 63.58 µg/mL (LuL), IC₅₀ 33.44 µg/mL (Col2), IC₅₀ 43.38 µg/mL (LNCaP), IC₅₀ 26.42 µg/mL (MCF-7) and IC₅₀ > 10.9 µg/mL (HUVEC) | [14]      |
| 49 | IC₅₀ > 57.4 µg/mL (KB, LuL, LNCaP), IC₅₀ 46.01 µg/mL (Col2), IC₅₀ 52.56 µg/mL (MCF-7), IC₅₀ 13.3 ± 0.62 µM (HCT116), IC₅₀ 7.24 ± 0.81 µM (A375) and IC₅₀ 18.3 ± 2.54 µM (A549) | [13,14] |
| 50/51 | IC₅₀ 5.22 µg/mL (KB), IC₅₀ 21.44 µg/mL (LuL), IC₅₀ 8.03 µg/mL (Col2), IC₅₀ 29.56 µg/mL (LNCaP), IC₅₀ 5.03 µg/mL (MCF-7) and IC₅₀ 3.28 µg/mL (HL60) | [14]      |
| 52/53 | IC₅₀ 54.97 µg/mL (KB), IC₅₀ 9.31 µg/mL (LuL), IC₅₀ 13.43 µg/mL (Col2), IC₅₀ 51.82 µg/mL (LNCaP) and IC₅₀ 12.18 µg/mL (MCF-7) | [14]      |
| 54/55 | IC₅₀ 5.28 µg/mL (KB), IC₅₀ 7.46 µg/mL (LuL), IC₅₀ 5.36 µg/mL (Col2), IC₅₀ 27.62 µg/mL (LNCaP), IC₅₀ 10.06 µg/mL (MCF-7), IC₅₀ 3.30 ± 0.06 µM (HCT116), IC₅₀ 3.38 ± 0.09 µM (A375) and IC₅₀ 10.4 ± 0.32 µM (A549) | [13,14] |
| 56 | IC₅₀ 6.11 µg/mL (KB), IC₅₀ 19.94 µg/mL (LuL), IC₅₀ 3.89 µg/mL (Col2), IC₅₀ 6.11 µg/mL (LNCaP) and IC₅₀ 6.39 µg/mL (MCF-7) | [14]      |
| 57 | IC₅₀ 6.71 µg/mL (KB), IC₅₀ 14.94 µg/mL (LuL), IC₅₀ 9.48 µg/mL (Col2), IC₅₀ 23.95 µg/mL (LNCaP), IC₅₀ 10.99 µg/mL (MCF-7), IC₅₀ 4.20 ± 0.30 µM (HCT116), IC₅₀ 4.25 ± 0.05 µM (A375) and IC₅₀ 20.8 ± 1.24 µM (A549) | [13,14] |
| 58 | IC₅₀ 3.07 µg/mL (KB), IC₅₀ 1.82 µg/mL (LuL), IC₅₀ 2.26 µg/mL (Col2), IC₅₀ 2.41 µg/mL (LNCaP), IC₅₀ 3.01 µg/mL (MCF-7) and IC₅₀ 0.63 µg/mL (HL60) | [14]      |
| 59 | IC₅₀ 2.61 µg/mL (KB), IC₅₀ 1.82 µg/mL (LuL), IC₅₀ 2.01 µg/mL (Col2), IC₅₀ 1.73 µg/mL (LNCaP) and IC₅₀ 2.26 µg/mL (MCF-7) | [14]      |
| No | Inhibitory concentrations (cell lines) | References |
|----|--------------------------------------|------------|
| 60 | IC$_{50}$ > 5.90 μg/mL (KB, Lu1, Col2, LNCaP and MCF-7) and IC$_{50}$ 57.01 μg/mL (HL60) | [14] |
| 61 | IC$_{50}$ > 65.0 μg/mL (HCT16, A375, A549) | [13] |
| 62/63 | IC$_{50}$ 9.80 ± 0.51 μM (HCT16), IC$_{50}$ 6.96 ± 0.23 μM (A375) and IC$_{50}$ 24.3 ± 1.42 μM (A549) | [13] |
| 64/65 | IC$_{50}$ > 52.9 μM (HCT16, A375 and A549) | [13] |
| 66/67 | IC$_{50}$ > 55.0 μM (HCT16, A375 and A549) | [13] |
| 68 | IC$_{50}$ 4.10 ± 0.13 μM (HCT16), IC$_{50}$ 3.60 ± 0.33 μM (A375) and IC$_{50}$ 7.15 ± 0.18 μM (A549) | [13] |
| 69 | IC$_{50}$ > 57.5 μM (HCT16, A375 and A549) | [13] |
| 70 | IC$_{50}$ 13.0 ± 0.17 μM (HCT16), IC$_{50}$ 10.4 ± 0.66 μM (A375) and IC$_{50}$ 24.5 ± 1.56 μM (A549) | [13] |
| 71 | IC$_{50}$ 18.3 ± 0.59 μM (HCT16), IC$_{50}$ 11.6 ± 1.45 μM (A375) and IC$_{50}$ 18.0 ± 2.80 μM (A549) | [13] |
| 72 | IC$_{50}$ 10.2 ± 0.1 μM (KB)$^{a}$, IC$_{50}$ 13.5 ± 0.5 μM (Vero), IC$_{50}$ 2.00 ± 0.16 μM (HCT16), IC$_{50}$ 15.0 ± 0.15 μM (A375), IC$_{50}$ 2.45 ± 0.24 μM (A549), IC$_{50}$ 1.18 μg/mL (KB)$^{b}$, IC$_{50}$ 1.64 μg/mL (Lu1), IC$_{50}$ 1.35 μg/mL (Col2), IC$_{50}$ 1.78 μg/mL (LNCaP), IC$_{50}$ 0.09 μg/mL (MCF-7), IC$_{50}$ 1.32 μg/mL (HUVEC) and IC$_{50}$ 0.66 μg/mL (HL60) | [7]$^h$; [13], [14]$^f$ |
| 75 | ED$_{50}$ 3.6 μg/mL (P-388), ED$_{50}$ 0.76 μg/mL (Col2), ED$_{50}$ 0.68 μg/mL (MCF-7) | [36] |
| 76 | IC$_{50}$ 4.6 μg/mL (KB), IC$_{50}$ 0.93 μg/mL (Hep-G2) and IC$_{50}$ > 5.0 μg/mL (RD) | [35] |
| 77 | IC$_{50}$ 4.3 μg/mL (KB), IC$_{50}$ 0.57 μg/mL (Hep-G2) and IC$_{50}$ 2.09 μg/mL (RD) | [35] |
| 79 and 107 | IC$_{50}$ > 128.0 μg/mL (MCF-7, LU, Hep-G2 and KB) | [37] |
| 83 and 87 | Inactive (KB and Vero) | [7] |
| 94 | > 5.0 μg/mL (KB and RD) and 1.5 μg/mL (Hep-G2) | [35] |
| 95 | IC$_{50}$ 0.7 μg/mL (KB), IC$_{50}$ 0.55 μg/mL (Hep-G2) and IC$_{50}$ 3.01 μg/mL (RD) | [35] |
| 116 | Inactive (KB, MCF-7 and NCI-H187) | [9] |
| 119 | Inactive (KB and Vero) | [7] |
| 123 | IC$_{50}$ 157.4 μM (KB), IC$_{50}$ 169.1 μM (MCF-7) and IC$_{50}$ 94.7 μM (NCI-H187) | [10] |
| 124 | IC$_{50}$ 20.3 μg/mL (KB), IC$_{50}$ 21.0 μg/mL (MCF-7) and IC$_{50}$ 17.1 μg/mL (NCI-H187) | [9] |
| 125 | IC$_{50}$ 179 μg/mL (KB), IC$_{50}$ 28.4 μg/mL (MCF-7) and IC$_{50}$ 15.9 μg/mL (NCI-H187) | [9] |
| 130 | IC$_{50}$ 18.4 μg/mL (KB), IC$_{50}$ 22.6 μg/mL (MCF-7) and IC$_{50}$ 20.6 μg/mL (NCI-H187) | [9] |
| 131 | IC$_{50}$ 12.9 μg/mL (KB), IC$_{50}$ 45.6 μg/mL (MCF-7) and IC$_{50}$ 16.7 μg/mL (NCI-H187) | [9] |
| 134 | IC$_{50}$ 31.4 μM (KB), IC$_{50}$ 56.2 μM (MCF-7) and IC$_{50}$ 61.3 μM (NCI-H187) | [10] |
| 139 | IC$_{50}$ 23.8 μg/mL (KB), IC$_{50}$ 24.4 μg/mL (MCF-7) and IC$_{50}$ 16.7 μg/mL (NCI-H187) | [9] |
| 140 | IC$_{50}$ 27.2 μM (KB), IC$_{50}$ 71.9 μM (MCF-7) and IC$_{50}$ 95.3 μM (NCI-H187) | [10] |
| 141 | IC$_{50}$ 95.9 μM (KB), IC$_{50}$ 142.7 μM (MCF-7) and IC$_{50}$ 115.9 μM (NCI-H187) | [10] |
| 143 | IC$_{50}$ 14.4 μg/mL (KB), IC$_{50}$ 13.0 μg/mL (MCF-7) and IC$_{50}$ 12.7 μg/mL (NCI-H187) | [9] |
| 145 | LD$_{50}$ 7.1 μg/mL | [5] |
| 146 | LD$_{50}$ 14.1 μg/mL | [5] |
| 147 | IC$_{50}$ 99.0 μM (KB), Inactive (MCF7) and IC$_{50}$ 48.9 μM (NCI-H187) | [40] |
| 148 | IC$_{50}$ 67.4 μM (KB), IC$_{50}$ 93.7 μM (MCF-7) and IC$_{50}$ 60.7 μM (NCI-H187) | [40] |
| 149 | IC$_{50}$ 57.2 μM (KB), IC$_{50}$ 84.8 μM (MCF-7) and IC$_{50}$ 66.3 μM (NCI-H187) | [40] |
| 150 | IC$_{50}$ 79.8 μM (KB), IC$_{50}$ 126.3 μM (MCF7) and IC$_{50}$ 61.1 μM (NCI-H187) | [40] |
| 152 | IC$_{50}$ 33.9 μM (KB), IC$_{50}$ 67.3 μM (MCF7) and IC$_{50}$ 27.0 μM (NCI-H187) | [40] |
| 153 | IC$_{50}$ 112.6 μM (KB), Inactive (MCF-7) and IC$_{50}$ 66.7 μM (NCI-H187) | [40] |
| 154 | IC$_{50}$ 59.9 μM (KB), IC$_{50}$ 92.0 μM (MCF7) and IC$_{50}$ 28.6 μM (NCI-H187) | [40] |
| 155 | IC$_{50}$ 43.3 μM (KB), IC$_{50}$ 129.7 μM (MCF-7) and IC$_{50}$ 32.3 μM (NCI-H187) | [40] |
| 158 | LD$_{50}$ 20.0 μg/mL | [5] |
| 161 | IC$_{50}$ 4.0 μM (KB), IC$_{50}$ 4.8 μM (MCF-7), IC$_{50}$ 4.2 μM (NCI-H187) and IC$_{50}$ 5.8 μM (Vero) | [38] |
| 162 | IC$_{50}$ 9.6 μM (KB), IC$_{50}$ 12.9 μM (MCF-7), IC$_{50}$ 6.5 μM (NCI-H187) and IC$_{50}$ 8.8 μM (Vero) | [38] |
Table 3: Continued.

| No  | Inhibitory concentrations (cell lines) | References |
|-----|--------------------------------------|------------|
| 163 | IC<sub>50</sub> 12.9 µM (KB), IC<sub>50</sub> 10.9 µM (MCF-7), IC<sub>50</sub> 11.4 µM (NCI-H187) and IC<sub>50</sub> 10.3 µM (Vero) | [38] |
| 164 | IC<sub>50</sub> 10.5 µM (KB), IC<sub>50</sub> 15.2 µM (MCF-7), IC<sub>50</sub> 8.7 µM (NCI-H187) and IC<sub>50</sub> 11.7 µM (Vero) | [38] |
| 166 | IC<sub>50</sub> 14.5 µM (KB), IC<sub>50</sub> 20.7 µM (MCF-7), IC<sub>50</sub> 11.5 µM (NCI-H187) and IC<sub>50</sub> 11.2 µM (Vero) | [38] |
| 167 | IC<sub>50</sub> 24.1 µM (KB), IC<sub>50</sub> 21.0 µM (MCF-7), IC<sub>50</sub> 14.7 µM (NCI-H187) and IC<sub>50</sub> 17.9 µM (Vero) | [38] |
| 168 | IC<sub>50</sub> 10.5 µM (KB), IC<sub>50</sub> 11.9 µM (MCF-7), IC<sub>50</sub> 6.8 µM (NCI-H187) and IC<sub>50</sub> 18.2 µM (Vero) | [38] |
| 174-176 | Inactive (KB, MCF-7, NCI-H187 and Vero) | [38] |
| 201-203 | Inactive (KB and Vero) | [7] |

**Plant extracts**

- **n-Hexane extract of M. sinensis**
  
  | IC<sub>50</sub> 86.6 µg/mL (MCF-7), IC<sub>50</sub> 78.33 µg/mL (LU), IC<sub>50</sub> 36.72 µg/mL (Hep-G2) and IC<sub>50</sub> 82.04 µg/mL (KB) |

- **Ethyl acetate extract of M. sinensis**
  
  | IC<sub>50</sub> 72.52 µg/mL (MCF-7), IC<sub>50</sub> 75.09 µg/mL (LU), IC<sub>50</sub> 42.50 µg/mL (Hep-G2) and IC<sub>50</sub> 59.13 µg/mL (KB) |

- **n-Butanol extract of M. sinensis**
  
  | IC<sub>50</sub> > 128.0 µg/mL (MCF-7 and KB) |

- **n-Hexane extract of M. smithiae**
  
  | ED<sub>50</sub> 9.07 µg/mL (P-388), ED<sub>50</sub> 12.0 µg/mL (KB), ED<sub>50</sub> 8.53 µg/mL (Col2), ED<sub>50</sub> 1.16 µg/mL (MCF-7), ED<sub>50</sub> 11.98 µg/mL (Lul1), ED<sub>50</sub> 13.31 µg/mL (T24), ED<sub>50</sub> 11.6 µg/mL (ASK) and ED<sub>50</sub> 6.74 µg/mL (Hek293) |

- **Ethyl acetate extract of M. smithiae**
  
  | ED<sub>50</sub> 2.07 µg/mL (P-388), ED<sub>50</sub> 5.45 µg/mL (KB), ED<sub>50</sub> 1.98 µg/mL (Col2), ED<sub>50</sub> 0.3 µg/mL (MCF-7), ED<sub>50</sub> 5.85 µg/mL (Lul1), ED<sub>50</sub> 3.29 µg/mL (T24), ED<sub>50</sub> 3.83 µg/mL (ASK) and ED<sub>50</sub> < 4.0 µg/mL (Hek293) |

- **Methanol and acetone extracts of M. smithiae**
  
  | Inactive (P-388, KB, Col2, MCF-7, Lul1, T24, ASK and Hek293) |

**Notes:** The results derived from different models.

M. fragrans and M. mollis, thereby suggesting the close relationship between them [9, 10, 24].

Besides geranylated homogentisic acids, oxo-protober-berine alkaloids, and flavonols, chemical constituents of *M. cuneata* leaf were also in association with the presence of the well-known lignan (+)-syringaresinol (119) [7]. In 2013, sixteen secondary metabolites, being isolated from methanol extracts of Thai *M. fragrans* leaf and stem in the work of Sawaddee and partners, were described as three lignans 117-118, 120 and thirteen neolignans 121, 124-125, 128-131, 135, 137-139, and 143-144 [9]. The new lignan (+)-3-hydroxyveraguisin (117) and its relatives 118 and 120 have been structurally established as 7S,8S,9R,9S-configuration (cis-H-7/H-7′, cis-H-′/H-8′, trans-H-7/H-8, and trans-H-8′/H-8′). The new neolignans 124-125, 128, 135, and 139 and two known ones 129-130 shared the same structure of three parts, 5-methoxy-phenylpropanoid unit, 2-methyl-1,4-dioxane unit, and phenyl ring linkage to carbon C-7. However, the absolute configurations were elucidated as 7S,8R for 124-125 and 129-130, 7S,8S for 128, and 7R,8R for 135 and 139, but the stereochemistry for new 8.0.A′-neolignans 137-138 and their analogs 138 and 144 could not be determined.

In the two years 2010 and 2013, Sawaddee and partners provided the results of the phytochemical isolation and NMR-structural elucidation of Thai *M. mollis*, in which one new neolignan of type dihydrobenzofuran (2S,3S)-2,3-dihydro-2-(4-methoxyphenyl)-3-methyl-5-benzofuran (127), one new 8.0.A′-neolignan (7S,8S)-three-DΔ8′-4-methoxyneolignan (132), and two known others 123 and 126 were isolated from twig; five new neolignans of type dihydrobenzofuran 7-methoxymiliumollin (133), 3′-methoxymiliumollin (134), 4′-O-methoxymiliumollin (136), miliumollin (140), miliumollinone (141); one new 8.0.A′-neolignan miliusanollin (142); and one known other (123) were derived from leaf [9, 10].

Neolignans of type dihydrobenzofuran from Thai plants have been shown to be associated with 2R,3R-absolute configuration (trans-H-2/H-3) in groups 122-123, 126, 133-134, and 140-141 and 2S,3S-absolute configuration (cis-H-2/H-3) in 127 and 136, while new compound 132 set up 7S,8S-model when compared to 7R,8R-model in 142 and 7S,8R-model in 143.

3.5. **Acetogenins and Lactones.** A bit of the attractive phytochemical outcome arose from the class of isolated acetogenins. As we know, acetogenins and their analogs are now remarkable characteristics of the family Annonaceae [47]. From Table 1 and Figure 5, isolated acetogenins existed in bark, stem bark, flower, and leaf of *M. velutina* species and they were new compounds except for goniothalamin (158). The most striking feature is that these isolated compounds
were able to form up to one or two triple bonds in a long aliphatic side chain terminated by γ-hydroxy (or γ-methoxyl)-γ-lactone unit, methyl group, or double bond.

Earlier phytochemical report by Jumana and coauthors (2000) showed that acetogenins A-B (145-146) obtained from Bangladeshi M. velutina species reached up to 0.00154% and 0.008% of extract weight, respectively [5]. However, NMR data of long alkyl side chain of these two compounds remain unknown. Paying attention to the result of phytochemical study on n-hexane extract of Thai M. velutina stem bark, based on repeating chromatographic columns on silica gel and sequential LiChrosorb RP-18 column techniques, we found that eight new compounds, alphabetically named cananginones A-I (147-155), have been successfully isolated as colorless viscous liquids [40]. Taking cananginone A (147) as an example, this new C23 linear olefinic acetogenin is accompanied by a variety of significant chemical shifts [(γ-methoxyl)-γ-lactone] unit established at δ_C 179.6 (C-1), δ_C 39.2 (C-2), δ_C 30.4 (C-21), δ_C 76.7 (C-22), δ_C 74.3 (C-23), and δ_C 59.5 (C-24); two double bonds and two triple bonds occurring at δ_C 65.1-146.6 ppm] [40]. Additionally, the positive OR value of +17.4 (c 0.206, CHCl_3) evidently confirmed 2R,22S-configuration compared with that of goniothalamusin (158) [+14.6 (c 0.206, CHCl_3)] [40]. Miliusolide and its dihydro derivatives 156-157 were also new derivatives of acetogenin detected in M. velutina stem bark [39]. Unfortunately, the trivial name ‘miliusolide’ was used for both metabolites 73 and 156 [30, 39].

In the light of phytochemical research, Wongsa and partners (2017) continuously provided the outcome relative to Thai M. velutina species (Figure 5) [38]. From n-hexane and ethyl acetate extracts of leaf of this plant, a rare class of eight bicyclic lactones with a C18 carbon backbone, trivially named...
velutinones A-H (161-168), were isolated. Similar to acetogenins, these compounds were collected with the physical property of colorless viscous liquids. Furthermore, they had shown the same feature in chemical structures, by which geranyl groups are located at carbon C-2a and the relative configuration at carbons C-2a and C-6a was syn-model (2aR,6aR).

In general, it is worth concluding that olefinic acetogenins with terminated γ-lactone and 2-geranylated bicyclic lactones indicated a great crucial role in chemotaxonomic aspect to recognize M. velutina. Lactones in genus Miliusa were also found in M. balansae; the two known compounds curcolide (159) and serralactone (160) were two components of the leaf of this plant, collected from Vietnam [11].

3.6. Styryls. Most of secondary metabolites of interest to chemists pointed out that styryl derivatives were found in genus Miliusa. Styryls presented as the significant constituents of the two species M. balansae and M. velutina [31, 32, 38, 41]. As shown in Table 1 and Figure 6, the three mono-styryls 169-171 and the five bis-styryls 172-176 have been updated. It is worth noting that yangonin (171) was, for the first time, reported from genus Miliusa, while the seven remaining isolates 169 and 172-176 were reported to be new compounds in nature.

The shrub tree M. balansae is widely distributed in Vietnam and China; chromatographic examination of the polar extract of leaf and branch of this plant yielded the two new mono-styryls 3,4-dimethoxy-6-styryl-pyran-2-one (169) and (2E,5E)-2-methoxy-4-oxo-6-phenyl-hexa-2,5-dienoic acid methyl ester (170) [31].

Regarding isolated compounds of type bis-styryls, the general chemical structure was designated by cyclobutyl nucleus, while side chains were made up of phenyl rings, α-pyronerings, and α,β-unsaturated ketones. In order to identify bioactive constituents, phytochemical investigation has been carried out on methanol-water extract (95:5, v/v) of Vietnamese M. balansae leaf and branch, which continuously demonstrated the existence of two bulk new bis-styryls miliubisstyryls A-B (172-173). Although NMR data of 172 were not completely assigned, the key NOE evidence
proposed that the relative configurations of 172 and 173 were identical, being trans-form for H-7/H-8 and H-7'/H-8', together with cis-form for H-8/H-7' and H-7/H-8'.

As mentioned above, M. velutina is a good reservoir of unique bicyclic lactones. From this plant, the three new bis-styryls velutinindimers A-C (174-176) were also separated [38]. According to this article, OR value approximately reached zero ([α]D +0.08 (c 0.63, MeOH-CHCl₃ 3:1)] and no Cotton effect was observed in CD spectrum which can be responsible for the symmetrical property of velutinindimer A (174) (compound containing a symmetrical plane). Similarly, the combination of the assignments of ¹H, ¹³C-NMR spectroscopic signals and the correlations in 2D-NMR data, as well as the most utilization of advantageous techniques such as the CD and X-ray measurements that considered velutinindimers B-C (175-176), were two racemic compounds.
and the relative configurations of these compounds were $S_5S,R_6S,R_785$ in compound 175 ($\alpha_1D + 0.08 (c 0.63, \text{MeOH-CHCl}_3 5:1)$) and $S_5R_6S,R_785$ in compound 176 ($\alpha_1D + 0.03 (c 0.23, \text{MeOH-CHCl}_3 9:1)$).

3.7. Terpenoids and Phenols. *M. balansae* species seems to be the most crucial objective in the contents of phytochemical researches related to plants of *Miliusa* species. Following the application of the variously chromatographic methods, norsesquiterpenoids of type megastigmanes, mono-phenols, and their glycosides have been determined as characteristics of genus *Miliusa*, especially *M. balansae* species. Eight terpenoids 177-185 and thirteen phenolic compounds 186-198 were summarized in Table 1 and Figure 7, which were newly isolated compounds or isolated for the first time from genus *Miliusa* [11,25,30,37,42].

Herein, mono-saccharide units of type $\beta$-D-glucopyranosyl parts and disaccharides units of type $\alpha$-D-apiofuranosyl-(1→6)-O-$\beta$-D-glucopyranosyl, $\beta$-D-apiofuranosyl-(1→6)-O-$\beta$-D-glucopyranosyl, $\beta$-xylopyranosyl-(1→6)-O-$\beta$-D-glucopyranosyl, $\alpha$-L-rhamnosyl-(1→6)-$\beta$-D-glucopyranosyl moieties are glycone parts linked to aglycones of terpenoids and phenols, whereas aglycones of phenols are mostly structurally formed by phenylethanoid nucleus.

Together with the one known terpenoid alangionoside B (177) and the four known phenolic glycosides cuchiloside (187), osmanthuside H (195), 1-($\alpha$-L-rhamnosyl-(1→6)-$\beta$-D-glucopyranosyl)-3,4,5-trimethoxybenzene (196), and 3,4,5-trimethoxyphenol-$\beta$-D-glucopyranoside (197), the phytochemical investigation of Chinese *M. balansae* species afforded one new megastigmane glycoside miliusoside C (182) and two new mono-phenols of type phenylethanoid glycosides miliusosides A-B (193-194) from 80% ethanol extract of dried stem [42]. The newly isolated compound 182 differed from its similar structure 177 in the orientation of D-apiosyl unit ($\alpha$-form in 182 and $\beta$-form in 177).

In Vietnamese *M. sinensis* leaf and branch, 24-methylenecycloartane-3$\beta,21$-diol (185) was the only triterpenoid reported to date, whereas the small-simple molecules 4-hydroxybenzonitrile (188), 4-hydroxybenzaldehyde (189), and isovanillin (191) were mono-phenols from *M. velutina* fruit [25,32,37].

Phytochemical analysis of methanol extract of Vietnamese *M. balansae* leaf has permitted the isolation and determination of the three new megastigmane glycosides milbasides A-C (179-181), in addition to the three analogs amelopsisionoside (178), myrsiniosides A and D (183-184), and one glucosylated phenol 1-(3-methylbutyryl)phloroglucinol-glucopyranoside (192) [11]. Structures 179-181 shared the same $E$-geometrical shape of double bond outside; in addition, due to the negative Cotton effect at around 240 nm ($\Delta\varepsilon$ ranged from $-1.73$ to $-3.27$), the absolute configurations of 179-180 were $2R,3S,5S,6S$, while compound 181 was proposed as $3S,5R,6R$ ($\Delta\varepsilon_{245nm} +3.27$). In the same manner, chemical shift of methylene group of bis(2-hydroxyphenyl) methyl ether (186) was higher than that of hydroxymethyl alcohol by 8 ppm, implying that compound 186 was a new symmetrical ether [30].
This review updated a phytochemical result of *M. mollis*; the twig of this plant also contained the two phenolic glycosides icariside D2 (190) and tyrosol 1-O-β-xylopyranosyl-(1→6)-O-β-D-glucopyranoside (198) [24]. The highlight in phenyl ring of aglycone of new compound 198 corresponded to A₂B₂ spin system [δH 7.10 (2H, d, J = 8.6 Hz, H-3 and H-5) and δH 6.95 (2H, d, J = 8.6 Hz, H-2 and H-6)], with glycone being remarked with two anomeric protons at δH 4.73 (1H, d, J = 7.3 Hz, H-1') and δH 4.17 (1H, d, J = 7.6 Hz, H-1').

3.8. Amine, Amide, Alcohol Derivatives and Miscellaneous Types. A phytochemical survey conducted by Yu and partners (2009) pointed out that *M. balansae* leaf, collected from China, has also been composed of one amine adenine riboside (199), and two amide allantoin (200), and uridine (204) (Figure 8) [26]. Although these compounds are now available in the natural plants, they were isolated as single compounds from genus *Miliusa* for the first time. Utilizing silica gel (63-200 μm) and sephadex LH-20 columns in the chromatographic isolation, three tyramine derivatives, *N*-trans-caffeoyltyramine (201), *N*-trans-coumaroyltyramine (202), and *N*-trans-feruloyltyramine (203), have been purified from acetone of *M. cuneata* air-dried twig [7]. Since then, acetone extract of *M. theorelii* stem and root was demonstrated to contain two isolates, 201 and 203 too [8].

Vietnamese *M. balansae* species might have been considered as a rich resource of diverse compounds. Based on the evidence of phytochemical findings and NMR explanations, six well-known alcohol derivatives, 205-210, were further obtained from the leaf of this plant for the first time [11]. Among them, β-D-glucopyranoside (Z)-3-hexenol (205) was a glycosylation of long n-alkyl side chain alcohol, while the five remaining ones 206-210 were categorized as two pairs of erythro and threo isomers of glycerols and one other glucosylated glycerol. They were erythro-guaiacylglycerol (206), three-guaiacylglycerol (207), erythro-1-C-syringylglycerol (209), three-1-C-syringylglycerol (210), and (L)-guaiacyl glycerol 2'-O-β-D-glucopyranoside (208), respectively. There were also records of these compounds from genus *Miliusa* for the first time. As can be seen, the difference of chemical components from Vietnamese and Chinese *M. balansae* species has been depending on geographic factor more often.

Besides the presence of the rare compounds of type homogentisic acid derivatives, the ethyl acetate extract of air-dried *M. velutina* fruit also consisted of furfural derivatives, in which three small molecules, 5-acetyloxymethylfurfural (211), 5-hydroxymethylfurfural (212), and 5-methoxyfurfural (213), were isolated [32]. Despite the fact that these compounds were formulated with a simple pattern, they were recorded from the plants of genus *Miliusa* for the first time.
As shown in Figure 9 and Table 1, the common chemical compounds of type phytosterols can be found in several *Miliusa* plants. For instance, *M. balansae* stem was reported to contain β-sitosterol (216), and its glucoside (217), or stigmasterol (219); this one turned out to be one of the components from both *M. sinensis* leaf and branch and *M. velutina* fruit and flower [25, 32].

Chromatographic separation of the extracts from *M. balansae* stem also led to the isolation and determination of two mono-saccharide D-glucose (214) and sucrose (220).
Figure 9: Other types from *Miliusa* species.

whereas *M. balansae* leaf and branch were accompanied by the existence of fatty acid octacosanoic acid (215) and benzoate sodium (218) [26, 32, 41].

3.9. Essential Oils. For a long time, there have been researching related to essential oils, which have frequently played an important role and been regarded as a branch of either phytochemistry or pharmacological products findings [1]. Many studies focused on the applications providing multifunction in healthcare problems, alternative medicines, food and drink manufacturers, or household cleaning products. Normally, the distillation method, often by using water steam, is a prompt and efficacious way; in addition, the extractions of solvent or floralsols have always been used depending on the raw materials. The systematic GC and GC-MS techniques are usually being used to identify volatile individuals. *Miliusa* species are also among the largest sources of this specific chemical compound. In the review of all circumstances, following the results of ethno-geographic distribution, species property, part use, extraction method, and GC-MS technical analysis, the results of studying essential oils of *Miliusa* species were compiled in Table 2. Essential oils studies on *Miliusa* plants are quite limited. There have been only three reports to date. Among forty-six members identified from essential oils of fresh leaf of, Quang Binh, Vietnamese *M. baillonii* species, the main constituent *Z*-citral reached the highest amount of 41.2% [28]. *M. sinensis* species, collected from Nghe An, Vietnam, is also likely to be a rich resource of essential oils. From this plant, 67.1% of a total of 95.1% of essential oils were sesquiterpene hydrocarbons [29]. Significantly, α-humulene and β-caryophyllene could be seen as the main components of oils of these two Vietnamese *Miliusa* plants (Table 2). In the same manner, the properties of plants, environmental factors, and collection time accounted for the differential components in essential oils of three, Queensland, Australian *Miliusa* plants, *M. brahei*, *M. horsfieldii*, and *M. traceyi* [27]. As can be seen from Table 2, these three species yielded oils, in which terpenoids predominated. α-Humulene, β-caryophyllene, and bicyclogermacrene achieved more than 10% of oils of *M. brahei*, while the major sesquiterpene of type caryophyllene derivatives ranged from 12% to 20%, present in *M. horsfieldii* oils; the highest components in oils of last plant *M. traceyi* encountered were the two isomers α- and β-pinene (approximately 19%). Of particular interest, β-caryophyllene was found to be one of the main compounds in all the five species (Table 2), which accounted for 10% to 20% of oils of *Miliusa* species.

4. Pharmacological Activities

4.1. Cytotoxic Activity. The plants of genus *Miliusa* included sets of variously useful isolated components to the experimentally cytotoxic targets. In the review of all conditions,
the cytotoxic results were briefly summarized in Table 3. Earlier report in 2000 by Jimana and partners mentioned the cytotoxicity of constituents from M. velutina species; the IC₅₀ results of tested compounds may run as acetogenin A (145) (IC₅₀ 7.1 μg/mL > acetogenin B (146) (IC₅₀ 14.1 μg/mL) > positive control vincristine (IC₅₀ 15.0 μg/mL) > goniophalamus (158) (IC₅₀ 20.0 μg/mL) [5]. Nine new acetogenins canagangonos A-I (147-155) were found to possess the weak IC₅₀ values of 16.6-129.7 μM or be inactive in the cytotoxic assay against three cancer cell lines KB, MCF7, and NCI-H187, when compared to those of reference compound doxorubicin (IC₅₀ 0.46-1.05 μM) [40].

Huong and partners (2004b) pointed out four flavonoids, 75-76 and 94-95, from Vietnamese M. balansae plant not just to show their powerful capacities (IC₅₀ < 5.0 μg/mL) in cytotoxic assay against the three cancer cell lines KB, Hep-G2, and RD, but also to emphasize that the introduction and modification of functional groups at carbon C-3, C-6, C-3', and C-4' were reasonable in the different results between pachypodol (95) and the remaining tested compounds 75-76 and 94 [30].

We then moved on to the demonstration of the proper agents from another Vietnamese medicinal plant, M. sinensis. n-Hexane and ethyl acetate extracts of this plant were moderately or weakly active against the four cancer cell lines MCF-7, LU, Hep-G2, and KB (IC₅₀ 42.5-86.6 μg/mL); in particular, their secondary metabolite liriodenine (12) induced the strong IC₅₀ values of 2.3-2.89 μg/mL towards MCF-7 and KB, but n-butanol extract and two isolated flavonoids, 3,5-dihydroxy-7,3'-4'-trimethoxyflavone (79) and 4',6'-dihydroxy-2',3',4'-trimethoxyhydrochalcone (107), did not show significant potency (IC₅₀ > 128.0 μg/mL) [37]. Likewise, the weak-polar extracts of type n-hexane and ethyl acetate extracts of Thai M. smithiae species generally revealed moderate cytotoxic results in the experiment with eight cell lines, P-388, KB, Col-2, MCF-7, Lu-1, T24, ASK, and Hek293, but better than the inactivation of the polar extracts of type acetone and methanol extracts [36]. It is worthy of note that ethyl acetate part and its isolated flavonoid ayanin (75) against MCF-7 with the IC₅₀ values of 0.3-0.68 μg/mL were comparable to positive control ellipticine (IC₅₀ 0.37 μg/mL) [36].

In a comparison between new dihydrobenzofuran neolignan 3' methoxymilumollin (134) and its analogs decurrenal (123), milumollin (140), and milumollinone (141) in the cytotoxic assay against the three cancer cell lines KB, MC7, and NCI-H187 (Table 3), methoxylation would lead to reducing the IC₅₀ values but the modification of allyl group did not seem to be the way of positive signal [9]. In another case, with the same test to KB, MC7, and NCI-H187 cell lines, the cytotoxic activity of chemical constituents of M. fragrans induced a clear arrangement as follows: 75R,R-8,0,4'-neolignan 143 (IC₅₀ 12.7-14.4 μg/mL) > dihydrobenzofuran neolignan 131 (IC₅₀ 12.9-16.7 μg/mL) > 7R,R,R-7,0,3',8,0,4'-neolignan 139 (IC₅₀ 16.7-23.8 μg/mL) > 75R,R-7,0,3',8,0,4'-neolignans 124-125 and 130 (IC₅₀ 15.9-28.4 μg/mL) > flavan 116 (inactive) [10].

Now, it is pretty noticeable that uncommon bicyclic lactones velutinindimers A-D and F-H (161-164 and 166-168) gave rise to a range of the IC₅₀ values from 4.0 μM to 24.1 μM in inhibiting three cancer cell lines, KB, MCF-7, and NCI-H187, and Vero cell line, while three new styryl derivatives 174-176 failed to do so [38]. As discussed above, leaf of M. cuneata was renowned as a reservoir of the diverse classes of secondary metabolites, but there has been a discrepancy between them in the cytotoxic assay [7]. In detail, either alkaloids, amides, flavonoids, or lignans inactivated towards two cell lines, KB and Vero, only geranylated homogentisic acid (+)-miliusol (72) and took part in suppressing these two cell lines with the IC₅₀ values of 10.2 ± 0.1 μM and 13.5 ± 0.5 μM, respectively.

Phytochemical studies on Miliusa plants have reached certain successes with isolating and identifying the presence of geranylated homogentisic acids, but more than ever, these compounds were further set to justify the cytotoxicity.

Isolated compounds 33-37 possessed the cytotoxic activities against the four cell lines KB, MCF-7, NCI-H187, and Vero with IC₅₀ values in the range of 3.8-40.4 μg/mL, and the failure of the two compounds 38-39 (IC₅₀ > 50.0 μg/mL) led to a hypothetical suggestion that the modification of double bond of geranyl unit would not be considered as a good method to promote the positive signal in assay [32].

Twenty-two homogentisic acid derivatives, comprising (+)-miliusate (40), (+)-miliusol (72), and serial (+)-miliusanes I-XX (41-60), have been screened by the cytotoxic assay with seven cancer cell lines, KB, Lul, Col2, LNCaP, MCF-7, HUVEC, and HL60, and the results were briefly summarized in Table 2 [14]. It is worth mentioning that in structure-biology relationship, at the dose of 20.0 μg/mL, (+)-miliusane V (45) was reported to be a nontoxic compound (IC₅₀ > 55.0 μg/mL) due to acetyl amide group. When comparing between (+)-miliusate (40) and (+)-miliusane IX (49), at carbon C-2, carboxylation was better than hydroxylation, but the opposite phenomenon was observed between (+)-miliusane VIII (48) and (+)-miliusol (72) since hydroxy group transferred into carbonyl group at carbon C-5. In accordance with the above results, hydroxylation, carboxylation, and epoxidation occurred at double bond of geranyl units of (+)-miliusanes X-XVII (50-57); the cytotoxicity did not enhance. Last but not least, γ-lactone ring opening, such as in compounds (+)-miliusanes XVIII-XIX (58-59), was shown not to render the cytotoxicity.

As part of the ongoing effort to improve the efficacy of milusane derivatives, recently, nineteen isolated compounds, (+)-miliusate (40), (+)-miliusane I-II, IX, XIV-XV, XVII, XXI-XXI (41-42, 49, 54-55, 57, 61-71), and (+)-miliusol (72), were continued to submit the cytotoxic assay with three cancer cell lines HCT116, A375, and A549 [13]. The results showed the positive signals when compounds 40-42, 54-55, 57, 68, especially (+)-miliusate (40), and (+)-miliusol (72) were demonstrated to be the most active with the IC₅₀ values of 1.0-5.0 μM.

4.2. Anticancer Activity. Anticancer experiments have been so far designated as a consequence of cytotoxicity. With the GI₅₀ values in the range of 0.03-4.79 μM, three geranylated derivatives of homogentisic acids, (+)-miliusate (40), (+)-milusane I (41), and (+)-miliusol (72), showed the potential
antitumor activities towards NCI-60 panel of human cancer cell lines, but were more active with HCT116 cell line [13]. In a comprehensive analysis, the main component of *Miluusa* plants, namely, (+)-miliusol (72), was highly recommended to anticancer drugs development. At the end of 21st day of *in vivo* anticancer treatment, this compound (20.0 mg/kg) induced the decrease in average size of excised HCT116 xenograft mouse tumor up to 72.7%, and the mechanism may be due to p21-dependent induction of cellular senescence rather than apoptosis [13].

4.3. Antimalarial Activity. With regard to antimalarial activities against *Plasmodium falciparum* strains TM4 and K1, the IC<sub>50</sub> values established a consistent arrangement as follows: standard compound cycloguanil (IC<sub>50</sub> 0.08 ± 0.01 μM and IC<sub>50</sub> 31.0 ± 8.4 μM) > geranlylated homogentisic acid (+)-miliusol (72) (IC<sub>50</sub> 11.1 ± 2.0 μM) and IC<sub>50</sub> 9.1 ± 3.1 μM) > new o xo-protoberine alkaloids 18-22, flavones 76 and 87, and amides 201 and 203 (IC<sub>50</sub> 19.3-41.4 μM and IC<sub>50</sub> 10.8-54.9 μM) > flavones 83 and 95, lignan 119 and amide 202 (inactive) [7]. It should be noted that among the four flavones 76, 83, 87, and 95, methylation at 5-OH and methoxylation at carbon C-6 can be responsible for promoting antimalaria, in contrast to the phenomenon dioxane-cyclization between two hydroxyl groups at C-3' and C-4', whereas hydroxylation and methoxylation at meta-position of caffeoyl unit induced the potential differences among the three amides 201-203.

In addition to antimalarial assay, two known isolated compounds 33-34 and new one miliusanone A (36) inhibited the growth of *P. falciparum* with the IC<sub>50</sub> values of 3.3-3.9 μg/mL but better than those of analogues miliusanone A (37) (IC<sub>50</sub> 5.2 μg/mL), miliusanol (35), and miliusanones C-D (38-39) (IC<sub>50</sub> > 10 μg/mL) [32]. From these data, it was also concluded that among the four geranylated homogentisic acid derivatives 33-34 and 36-37, the number of ester groups in the structure seemed to be the main for the outcome.

Serial new acetogenins cananginones A-1 (147-150) and 152-155 failed to inhibit *P. falciparum* except for cananginone E (151) (IC<sub>50</sub> 24.4 μM) [40]. Comparing between the structure 151 and the close group of compounds 152 and 154-155, dihydroxylation of double bonds and methylene reduction would not be facilitated.

Three new bulk steryl derivatives, velutinindimers A-C (174-175), established better IC<sub>50</sub> values in the range of 5.4-6.4 μM towards *P. falciparum* than new unique bicyclic lactones velutinones B-D, G, and H (162-164 and 167-168) (IC<sub>50</sub> 7.3-10.0 μM) [38].

4.4. Antifungal and Antimycobacterial Activities. In the search for natural products against DNA repair mutant in the yeast strain *Saccharomyces cerevisiae*, the MeCOEt extract of *M. Cf. banacea* root showed inhibited *rad* 52, top 1 (IC<sub>12</sub> 2000 μg/mL), but failed to do so with *rad* 52 and *rad* (IC<sub>12</sub> > 8000 μg/mL) [4]. In the meantime, new alkaloid 10-hydroxylirodeine (7) and positive control camptothecin afforded the respective IC<sub>12</sub> values of 72 μg/mL and >20 μg/mL in suppressing *rad* 52, top 1, being better than that of 10-methoxylirodeine (14) (IC<sub>12</sub> 113 μg/mL).

The MIC values ranging from 4.0 μg/mL to >128 μg/mL were the results when using chalcone pashanone (109) and flavanone 5-hydroxy-6,7-dimethoxyflavonone (110) against thirteen human pathogenic fungi, *Candida albicans* ATCC10231, *Candida krusei* ATCC6258, *Candida lusitaniae* ATCC42720, *Candida tropicalis* ATCC13803, *Cryptococcus gattii* R265, *Cryptococcus gattii* WM276, *Cryptococcus neoformans* JEC21, *Cryptococcus neoformans* ATCC35656, *Cryptococcus neoformans* var. grubii H99, *Aspergillus fumigatus* ATCC16424, and *Trichophyton mentagrophytes* ATCC9533 [6].

The effect of new cananginones H-1 (154-155) on fungal *C. albicans* has been shown to be associated with the IC<sub>50</sub> values of 75.2 μM and 37.4 μM, respectively, but new acetogenins cananginones A-G (147-153) did not appear active [40]. Herein, the reason is opposite to antimalarial analysis when four structures 151-152 and 154-155 were considerably compared.

The global health problem in developing countries is becoming increasingly involved in growing and expanding of microbacteria. Historical records have accumulated evidence showing that the use of traditional antibiotics, which are derived from synthetic substances, is always accompanied by a long duration of treatment, high cost, and drug resistance [48]. Therefore, calls for new antibiotic drugs from natural sources in the fight against multidrug-resistant bacteria are always strategy.

In a short communication, various components from *M. tomentosa* species suppressed the growth of several kinds of bacteria and fungi, but the most significant finding is that leaf volatile oil extract reduced the growth of bacterium *Bacillus subtilis* NCIM 2250 and fungal *C. albicans* NCIM 3471 with the same MIC value of 0.62 mg/mL, being better than those of leaf aqueous extract (2.5 mg/mL and 5.0 mg/mL, respectively) [49].

Acetogenin A (145) and gonothalamin (158) are associated with the moderate antibacterial activity with diameters of the inhibitory zone of 9-14 mm against positive Gram bacteria *Bacillus cereus*, *Staphylococcus aureus*, and *Streptococcus β-haemolyticus* and 9-11 mm against negative Gram bacteria *Salmonella typhi*, *Shigella flexneri*, and *Shigella dysenteriae*, whereas acetogenin A (146) only influenced *B. cereus* with diameter zone of 11 mm [5].

The MIC values ranged from 32.0 to 64.0 μg/mL, which were the moderate antibacterial result of two geranylated homogentisic acids, 33 and 35, repellant positive Gram bacteria *B. cereus* DMST 5040, *S. aureus* DMST 8013, and methicillin resistant *S. aureus*. Meanwhile, two other geranylated homogentisic acids, 34 and 36, and two styrils, 171 and 175, were only found to be associated with the MIC values of 64.0-128.0 μg/mL against *B. cereus* DMST 5040 [32]. It was, therefore, concluded that geranylated homogentisic acids seemed to be better candidates for this problem rather than steryl derivatives.

At the same time, compound 33 revealed the MIC value of 50 μg/mL to treat *Mycobacterium tuberculosis* H37Ra compared with that of the similar structures 34-39 (MIC > 50 μg/mL) [32]. Apparently, substituting groups R<sub>1</sub> and R<sub>2</sub> demonstrated the great role affecting the results.
Two unique bicyclic lactones, 161-162, resisted the growth of *M. tuberculosis* with the MIC values of 43.4 μM and 82.1 μM, respectively, but analogs 163-168 showed no activity. It is possible to note that epoxidation and hydroxylation would not be good circumstances to have positive signals in the activity [38].

4.5. Anti-Inflammatory Activity. Inflammation can be seen as a part of the complex biological response of the body tissues to harmful stimuli, such as irradiation, physical damage, metabolic overload, or infection [20]. Nowadays, modern diseases, for instance, cardiovascular and neurodegenerative disorders, are closely related to inflammation. Suppressing NO production is recognized to be a useful strategy for this problem.

On the screening of anti-inflammatory activity, by using mode of lipopolysaccharides (LPS) (1.0 μg/mL)-induced NO production in microglial RAW 264.7 cells, megastigmane glycosides milbasides A-C (179-181), alcohols β-D-glucopyranoside (Z)-3-hexenol (205), and (L)-guaiaacyl gerol 2'-O-β-D-glucopyranoside (208), at a concentration of 20.0 μM, together with flavan (-)-epicatechin (116) and megastigmane glucoside myrsinonioside D (184), at a concentration of 40.0 μM, indicated potent inhibitory activity comparable with or better than positive control sulfuretin (81.3 ± 4.9% at 20.0 μM) [11].

Because of glycosylation, NO inhibitory capacity compound 208 was generated 2.0-2.5 times higher than those of *erythro-* and *threo*-guaiaacylglycerol (206-207) (48.4 ± 3.9%) [11].

4.6. Antiviral Activity. At the dose of 100 μg/mL, methanol extracts from stem and leaf of *M. fragrans* showed the IC₅₀ values of 60-80 μg/mL in the antiviral experiment against HSV-1 and HSV-2. Meanwhile, in contrast to the inactive results of 116-118, 120-121, 124, 128-130, 135, 139, and 143-144, (+)-4-O-demethylusiderin C (125) and licarin A (131) were found to possess the same IC₅₀ values of 62.5-66.7 μg/mL (HSV-1) and 875 μg/mL (HSV-2) [9]. It was figured out that 7,8R,7-O,3',8,6,4'-neolignans should be the best choice for this model. Furthermore, by comparing 124-125 and 129-130, their antiviral outcomes closely depended on two functional groups, R₁ and R₂ (Figure 4).

4.7. Antioxidant Activity. Although phytochemical investigation of *M. wayanadica* species has not yet been performed extensively, its ethanol leaf extract was observed to be equivalent to or better than positive controls in antioxidant assays. For instance, in DPPH assay, the IC₅₀ value of 465 μg/mL arising from *M. wayanadica* ethanol leaf extract was comparable with those of standard compounds BHT (570 μg/mL) and BHA (615 μg/mL); with regard to the ferric reducing antioxidant examination, the IC₅₀ values for these three objects reached 600 μg/mL, 835 μg/mL, and 870 μg/mL, respectively [50].

4.8. Enzyme Acetylcholine Inhibitory Activity. To date, only one research dealt with the use of chemical constituents from *M. thorelii* species exploring the potency of *Miliusa* secondary metabolites in acetylcholinesterase inhibitory activity. The results pointed out that alkaloids (the inhibitory capacity of new oxo-protoberberines 23-24 and known one 28 reached the significant range of 27.93%-50.17%) were promising agents rather than flavonoids (the inhibitory percentages of <10%-38.68% were for 80-83, 85-86, 88-91, 93, 95-99, and 101-102) or amides (tested compounds 201 and 203 were inactive, <10%) [32].

4.9. Cardiac Activity. Chrysosplenol C (77), a flavonol, isolated from *M. balansae*, proved to be an essential backbone to induce a positive inotropic effect on rat ventricular myocytes [12]. This compound caused the contractive percentage of ventricular cell and the active percentage of cardiac myosin ATPase up to 53.0 ± 4.07% at 50 μM and 28.1 ± 1.20% at 10 μM, respectively, compared with those of positive control omeprazol and meparb [59.3 ± 2.60% at 400 μM and 80.4 ± 2.89% at 10 μM, respectively] [12].

5. Conclusion

Taken together, *Miliusa* species have been fully researched in both phytochemical and pharmaceutical aspects, and a general view of the previous results has been outlined in the current paper. This review mostly focused on the knowledge about botanical description, phytochemistry, and biological evaluation. Basic findings might be concluded as below:

(i) *Miliusa* plants are widely distributed in tropical and subtropical regions, particularly Asia mainland.

(ii) Based on morphological analysis and the heavy support of DNA-barcoding techniques, the number of new *Miliusa* plants discovered increased more often. Up to present, approximately sixty species were identified.

(iii) More than ten *Miliusa* species were highlighted in studying phytochemical and pharmacological aspects. Among them, *Miliusa* plants, collected from Vietnam, Thailand, and China, were major objectives for phytochemical investigations.

(iv) A variety of secondary metabolites have been successfully isolated. In the current paper, we draw a list of twenty-two hundred isolated compounds. Chemical constituents derived from *Miliusa* have fallen into multiple classes of compounds, such as alkaloids, flavonoids, terpenoids, styrals, and lactones, but serial novel derivatives of geranylated homogentisic acid could be seen as biomarkers to recognize *Miliusa* species.

(v) The geographic factors, environment, and collection time can be responsible for the difference in chemical components of each country. For instance, Thai *M. mollis* and *M. fragrans* plants established the high amount of lignans and neolignans whereas some Vietnamese *Miliusa* plants were characterized by the rich flavonoids, terpenoids, or miliusanes.
(vi) Naturally occurring isolated compounds and plant extracts of this genus have been subjected to various pharmacological types, but cytotoxic assay seemed to be the main content of previous researches.

(vii) It was also observed that the biological activation or inactivation of tested compounds closely depended on the key role of functional groups in the chemical structures.

(viii) β-caryophyllene (10%-20%) was considered as major component in essential oils extracted from Vietnamese and Australian Miliusa plants.

Finally, plant growing proposals, scientific assessments, and extensive phytochemical discoveries on this valuable source ought to be a willingness for drug leads and future pharmaceuticals. Bioactive compounds, in vitro and in vivo pharmaceutical analyses, clinical applications, and unknown mechanism explanations are expected.

Abbreviations

HPLC: High performance liquid chromatography
GC-MS: Gas chromatography-mass spectrum
NMR: Nuclear magnetic resonance
UV-Vis: Ultraviolet-visible
IR: Infrared
OR: Optical rotation
CD: Circular dichroism
LPS: Lipopolysaccharide
BHA: Butylated hydroxyanisole
BHT: Butylated hydroxytoluene
HSV-1 and HSV-2: Herpes simplex virus-1 and herpes simplex virus-2
MCF-7: Human breast carcinoma cell line
A549 and LU: Human lung carcinoma cell lines
Hep-G2, KB: Human oral epidermoid carcinoma cell line
Vero: Kidney epithelial cell line
NCI-H187, Col2, and HCT116: Human colon carcinoma cell lines
LNCaP: Human prostate carcinoma cell line
HUVEC: Human umbilical vein endothelial cell line
HL60: Human promyelocytic leukemia cell line
A375: Human melanoma carcinoma cell line
P-388: Human murine lymphocytic leukemia cell line

ASK: Rat glioma cell line
Hek293: Noncancerous human embryonic kidney cell line
T24: Human urinary bladder cancer cell line.

Conflicts of Interest

The author declares no conflicts of interest.

Acknowledgments

This work was supported by a grant from Vietnam Academy of Science and Technology, Vietnam, 2019.

References

[1] N. The Son, “Secondary metabolites of genus pandanus - an aspect of phytochemistry,” Mini-Reviews in Organic Chemistry, vol. 16, no. 1, 2019.
[2] N. T. Son and A. I. Elshamy, “Flavonoids and other non-alkaloidal constituents of genus erythrina: a detailed account of phytochemical review,” Current Organic Chemistry, vol. 23, no. 1, 2019.
[3] T. Chaowasku and P. J. Kessler, “Miliusa cambodgensis sp. nov. (Annonaceae) from Cambodia and M. astiana, M. ninbinhensis spp. nov. from Vietnam,” Nordic Journal of Botany, vol. 32, no. 3, pp. 298–307, 2014.
[4] T. Chaowasku and P. J. A. Kessler, “Isolation of bioactive and other o xoaporphine alkaloids from two annaceous plants, Xylopia aethiopica and Miliusa CF. banacea,” Journal of Natural Products, vol. 57, no. 1, pp. 68–73, 1994.
[5] S. Jumana, C. M. Hasan, and M. A. Rashid, “Antibacterial activity and cytotoxicity of Miliusa velutina,” Fitoterapia, vol. 71, no. 5, pp. 559–561, 2000.
[6] W. J. Lee, J. S. Moon, Y. T. Kim, T. T. Bach, D. V. Hai, and S. U. Kim, “Inhibition of the calcineurin pathway by two flavonoids isolated from miliusa sinensis finet & gagnep,” Journal of Microbiology and Biotechnology, vol. 26, no. 10, pp. 1696–1700, 2016.
[7] T. Promchai, A. Jaidee, S. Cheenpracha et al., “Antimalarial o xoaporphine alkaloids from the leaves of Miliusa cuneata,” Journal of Natural Products, vol. 79, no. 4, pp. 978–983, 2016.
[8] T. Promchai, T. Saeong, K. Ingkaninan, S. Laphookhieo, S. G. Pynef, and T. Limtharakul, “Acetylcholinesterase inhibitory activity of chemical constituents isolated from Miliusa thorelii,” Phytochemistry Letters, vol. 23, pp. 33–37, 2018.
[9] K. Sawasdee, T. Chaowasku, V. Lipipun, T. Dufat, S. Michel, and K. Likhitwitayawuid, “New neolignans and a lignan from Milisusa fragrans, and their anti-herpetic and cytotoxic activities,” Tetrahedron Letters, vol. 54, no. 32, pp. 4259–4263, 2013.
[10] K. Sawasdee, T. Chaowasku, V. Lipipun, T. Dufat, S. Michel, and K. Likhitwitayawuid, “Neolignans from leaves of Milisusa mollis,” Fitoterapia, vol. 85, pp. 49–56, 2013.
[11] N. P. Thao, B. T. T. Luyen, B. H. Tai et al., “Chemical constituents of Milisusa balansae leaves and inhibition of nitric oxide production in lipopolysaccharide-induced RAW 264.7 cells,” Bioorganic & Medicinal Chemistry Letters, vol. 25, pp. 3859–3863, 2015.
[12] E. Venkateswararoa, M. J. Son, N. Sharma et al., “Exploration of pharmacophore in chryosplenol C as activator in ventricular
[47] V. Seidel, F. Bailleul, and P. G. Waterman, "Goniothalamusin, a linear acetogenin from Goniothalamus gardneri," *Phytochemistry*, vol. 52, no. 6, pp. 1101–1103, 1999.

[48] N. T. Son, M. Oda, N. Hayashi et al., "Antimicrobial activity of the constituents of Dalbergia tonkinensis and structural-bioactive highlights," *Natural Product Communications (NPC)*, vol. 13, no. 2, pp. 157–161, 2018.

[49] V. B. Badgujar and S. J. Surana, "Comparative investigation on antimicrobial property of Miliusa tomentosa leaf oil and leaf extract," *Iranian Journal of Pharmacology & Therapeutics*, vol. 10, no. 1, pp. 7–10, 2011.

[50] P. Favaz, P. A. Thomas, D. G. Thomas Parambi, K. B. Anil, A. Baby, and N. Rajan, "Histological evaluation, antioxidant and cytotoxic studies of Miliusa wayanadica," *IOSR Journal of Pharmacy and Biological Sciences*, vol. 9, no. 5, pp. 50–60, 2014.