Review

A Review on the Phytochemistry, Pharmacology, and Pharmacokinetics of Amentoflavone, a Naturally-Occurring Biflavonoid

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Abstract: Amentoflavone (C30H18O10) is a well-known biflavonoid occurring in many natural plants. This polyphenolic compound has been discovered to have some important bioactivities, including anti-inflammation, anti-oxidation, anti-diabetes, and anti-senescence effects on many important reactions in the cardiovascular and central nervous system, etc. Over 120 plants have been found to contain this bioactive component, such as Selaginellaceae, Cupressaceae, Euphorbiaceae, Podocarpaceae, and Calophyllaceae plant families. This review paper aims to profile amentoflavone on its plant sources, natural derivatives, pharmacology, and pharmacokinetics, and to highlight some existing issues and perspectives in the future.

Keywords: amentoflavone; biflavonoid; natural derivatives; pharmacokinetics; pharmacology; phytochemistry

1. Introduction

Amentoflavone (C30H18O10) is a common biflavonoid chemically named as 8-[5-(5,7-dihydroxy-4-oxo-4H-chromen-2-yl)-2-hydroxyphenyl]-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one, which naturally occurs in many plants. It is also considered as an apigenin dimer linked by a C3′-C8′ covalent bond (Figure 1). This compound was firstly isolated by Okigawa and his colleagues in 1971 from three plants of the Selaginella species (Selaginella tamariscina (Beauv.) Spring, Selaginella nipponica, and Selaginella pachystachys) [1]. From then on, phytochemical researchers have isolated and identified this biflavonoid from more than 120 plants, some of which have been used as traditional folk medicines in many regions of the world for even thousands of years. With the development of modern pharmacology, more and more evidence has proved many of the bioactivities of amentoflavone, including anti-oxidant [2], anti-inflammatory [3], anti-senescence [4], anti-tumor [5], anti-virus [6], and anti-fungal [7] effects, as well as therapeutic effects on the central nervous system [8] and cardiovascular system [9], etc. With its good pharmacological performance and high content, amentoflavone is even listed as the chemical marker of Selaginellae Herba (“Juanbai” in Chinese, which represents the whole plants of Selaginella tamariscina or Selaginella pulvinata) for quality evaluation in the Chinese Pharmacopoeia [10].

Due to its large range of bioactivities and originating from nature, amentoflavone has attracted increasing focus from a number of research fields. Here, in this paper, we aim to provide a review...
of this naturally-occurring biflavonoid, describing its sources, natural derivatives, pharmacological effects, and pharmacokinetics, and to help researchers understand and utilize it in a better way.

2. Sources

As a polyphenolic compound, amentoflavone exists in a large number of plants (Table 1). To our knowledge, the major sources are the plants of Calophyllaceae, Clusiaceae, Cupressaceae, Euphorbiaceae, and Selaginellaceae families, and Calophyllum, Garcinia, and Selaginella species, etc. Some of these plants have been used as folk phytomedicines for a very long time, such as *Gingko biloba*, *Lobelia chinensis*, *Polygala sibirica*, *Ranunculus ternatus*, *Selaginella pulvinata*, *Selaginella tamariscina* for traditional Chinese medicines (TCMs), *Calophyllum inophyllum*, *Selaginella bryopteris* for traditional Indian medicines, *Byronima intermedia* for traditional American medicine, and *Cnestis ferruginea* and *Drypetes gerrardii* for traditional African medicines.

| No. | Plant                     | Family       | Part            | References |
|-----|--------------------------|--------------|-----------------|------------|
| 1   | *Amanoa almerindae*      | Phyllanthaceae| aerial parts    | [11]       |
| 2   | *Alchornea glandulosa*   | Euphorbiacea | leaves          | [12]       |
| 3   | *Alchornea triplinervia* | Euphorbiacea | leaves          | [13]       |
| 4   | *Altris spica*           | Liliaceae    | herbs           | [14]       |
| 5   | *Allanblackia monticola* | Guttiferae   | leaves          | [15]       |
| 6   | *Androsace umbellata*    | Primulaceae  | whole plants    | [16]       |
| 7   | *Antidesma bunius*       | Phyllanthaceae| leaves          | [17]       |
| 8   | *Antidesma laciniatum*   | Euphorbiacea | leaves          | [18]       |
| 9   | *Biophytum sensitivum*   | Oxalidaceae  | roots           | [19]       |
| 10  | *Biota senipervires*     | Cupressaceae | leaves          | [20]       |
| 11  | *Byronima crassa*        | Malpighiacea | leaves          | [21]       |
| 12  | *Byronima intermedia*    | Malpighiacea | leaves          | [22]       |
| 13  | *Caesalpinia pyramidalis*| Leguminosae  | leaves          | [23]       |
| 14  | *Callitris rhomboidea*   | Cupressaceae | leaves          | [24]       |
| 15  | *Calocedrus microlepica var. formosana formosana* | Cupressaceae | leaves          | [25]       |
| 16  | *Calophyllum brasiliense*| Calophyllaceae| leaves          | [26]       |
| 17  | *Calophyllum ferrugineum*| Calophyllaceae| barks, leaves   | [27]       |
| 18  | *Calophyllum flavoratum* | Calophyllaceae| leaves          | [28]       |
| 19  | *Calophyllum incrassatum*| Calophyllaceae| barks, leaves   | [29]       |
| 20  | *Calophyllum inophyloide*| Calophyllaceae| heartwood       | [30]       |
| 21  | *Calophyllum inophyloide*| Calophyllaceae| leaves          | [31]       |
| 22  | *Calophyllum membranaceum*| Guttiferae | leaves          | [33]       |
| 23  | *Calophyllum pinetorum*   | Guttiferae   | stem barks, leaves | [34]     |
Table 1. Cont.

| No. | Plant               | Family          | Part               | References |
|-----|---------------------|-----------------|--------------------|------------|
| 24  | Calophyllum rivulare| Calophyllaceae  | leaves             | [35]       |
| 25  | Calophyllum symingtonianum | Calophyllaceae | barks, leaves    | [36]       |
| 26  | Calophyllum venulosum | Calophyllaceae  | leaves             | [37]       |
| 27  | Campylospermum calanthum | Ochnaceae   | leaves             | [38]       |
| 28  | Campylospermum manntii | Ochnaceae     | leaves             | [39]       |
| 29  | Canarium album      | Burseraceae    | leaves             | [40]       |
| 30  | Canarium pinela     | Burseraceae    | fruits             | [41]       |
| 31  | Canarium schweinfurthii | Burseraceae  | fruits             | [42]       |
| 32  | Casearia clarkei    | Flacourtiaceae | leaves             | [43]       |
| 33  | Celaenodendron mexicanum | Euphorbiaceae | leaves, twigs      | [44]       |
| 34  | Cephalotaxus fortunei | Cephalotaxaceae | leaves         | [45]       |
| 35  | Cephalotaxus korana | Cephalotaxaceae | leaves, twigs    | [46]       |
| 36  | Cephalotaxus olivieri | Cephalotaxaceae | leaves           | [47]       |
| 37  | Chamaecyparis obtusa | Cupressaceae   | leaves             | [48]       |
| 38  | Chrozophora tinctoria | Euphorbiaceae | aerial parts       | [49]       |
| 39  | Cnestris ferruginea | Connaraceae    | roots              | [50]       |
| 40  | Cunninghamia lanceolata | Taxodiaceae | branches, leaves  | [51]       |
| 41  | Cupressocyparis leyladii | Cupressaceae | leaves             | [52]       |
| 42  | Cupressus chengiana | Cupressaceae   | -                  | [53]       |
| 43  | Cupressus sempervirens | Cupressaceae | leaves             | [54]       |
| 44  | Cynas badowiana     | Cycadaceae     | cones              | [55]       |
| 45  | Cynas circinalis    | Cycadaceae     | leaflets           | [56]       |
| 46  | Cynas panzhihuaensis| Cycadaceae     | flowers            | [57]       |
| 47  | Cynas pectinata     | Cycadaceae     | fruits             | [58]       |
| 48  | Cynas revoluta      | Cycadaceae     | leaflets           | [59]       |
| 49  | Dacrydium araucaroides | Podocarpaceae | leaves             | [60]       |
| 50  | Decussocarpus rospigliosii | Podocarpaceae | leaves             | [61]       |
| 51  | Diospyros rufescens | Euphorbiaceae  | aerial parts       | [62]       |
| 52  | Dorstenia barteri   | Moraceae       | twigs              | [63]       |
| 53  | Drupetes gerrardii  | Euphorbiaceae  | stems              | [64]       |
| 54  | Drupetes hainanensis| Euphorbiaceae  | leaves, stems      | [65]       |
| 55  | Elaterispermum tapos | Euphorbiaceae | stems, leaves      | [66]       |
| 56  | Galeobdolon chinense| Labiaceae      | whole plants       | [67]       |
| 57  | Garcinia bakeriana  | Clusiaceae     | leaves             | [68]       |
| 58  | Garcinia brasiliensis| Clusiaceae     | branches, leaves   | [69]       |
| 59  | Garcinia brevipedicellata | Clusiaceae | stem heartwood    | [70]       |
| 60  | Garcinia cova       | Clusiaceae     | fruits             | [71]       |
| 61  | Garcinia intermedia | Clusiaceae     | leaves             | [72]       |
| 62  | Garcinia livingstonei| Clusiaceae    | leaves             | [73]       |
| 63  | Garcinia merguensis | Clusiaceae     | twigs              | [74]       |
| 64  | Garcinia subelliptica| Clusiaceae     | leaves             | [75]       |
| 65  | Garcinia xanthochymus| Clusiaceae    | fruits             | [76]       |
| 66  | Gingko biloba      | Ginkgoaceae    | leaves             | [77]       |
| 67  | Hypericum connatum  | Hypericaceae    | aerial parts       | [78]       |
| 68  | Hypericum perforatum| Hypericaceae   | aerial parts       | [79]       |
| 69  | Hyeronima alchorneoides | Euphorbiaceae | leaves             | [80]       |
| 70  | Juniperus occidentalis | Cupressaceae  | leaves             | [81]       |
| 71  | Juniperus rigida    | Cupressaceae   | leaves, twigs      | [82]       |
| 72  | Lantana lanata      | Lantaneae      | whole plants       | [83]       |
| 73  | Labelia chinensis   | Campanulaceae  | whole plants       | [84]       |
| 74  | Lonicera chrysanth  | Caprifoliaceae | aerial parts       | [85]       |
| 75  | Lonicera macrinhoides| Caprifoliaceae | stems, leaves      | [86]       |
| 76  | Lonicera similes    | Caprifoliaceae | flower buds        | [87]       |
| 77  | Lucemborgia nobilis | Ochnaceae      | branches, leaves   | [88]       |
| 78  | Lysimachia christinae| Primulaceae    | whole plants       | [89]       |
| 79  | Mangifera indica    | Anacardiaceae  | leaves             | [90]       |
Table 1. Cont.

| No. | Plant             | Family               | Part                | References |
|-----|-------------------|----------------------|---------------------|------------|
| 80  | Manihot esculenta | Euphorbiaceae        | stems               | [89]       |
| 81  | Microbiota decussata | Cupressaceae       | leaves              | [90]       |
| 82  | Nandina domestica | Berberidaceae        | fruits              | [91]       |
| 83  | Nanuza plicata    | Velloziaceae         | leaves              | [92]       |
| 84  | Ochna schweinfurthiana | Ochnaceae      | barks               | [5]        |
| 85  | Ouratea parviflora| Ochnaceae            | leaves              | [93]       |
| 86  | Ouratea semiserata| Ochnaceae            | branches, leaves    | [94]       |
| 87  | Ouratea sulcata   | Ochnaceae            | aerial parts        | [95]       |
| 88  | Pistacia chinensis| Anacardiaceae        | inflorescences      | [96]       |
| 89  | Podocarpus imbricatus | Podocarpaceae    | barks, leaves       | [97]       |
| 90  | Polygala sibirica | Polygalaceae         | aerial parts        | [98]       |
| 91  | Ranunculus ternatus| Ranunculaceae      | root tubers         | [99]       |
| 92  | Retrophylllum rospigliosii | Podocarpaceae | leaves              | [100]      |
| 93  | Rhus pyroides     | Anacardiaceae        | leaves              | [101]      |
| 94  | Rhus succedaneae  | Anacardiaceae        | leaves, twigs       | [102]      |
| 95  | Sabina pingii var. wilsonii | Cupressaceae | leaves, twigs       | [103]      |
| 96  | Sabina sinoalpina | Cupressaceae         | -                   | [104]      |
| 97  | Sabina vulgaris   | Cupressaceae         | leaves              | [105]      |
| 98  | Selaginella breptetis | Selaginellaceae    | whole plants        | [106]      |
| 99  | Selaginella chrysocaulos | Selaginellaceae | whole plants        | [106]      |
| 100 | Selaginella deliciata | Selaginellaceae    | whole plants        | [107]      |
| 101 | Selaginella denticulata | Selaginellaceae  | whole plants        | [108]      |
| 102 | Selaginella dodderleitii | Selaginellaceae   | whole plants        | [109]      |
| 103 | Selaginella involvens | Selaginellaceae    | whole plants        | [110]      |
| 104 | Selaginella labordei | Selaginellaceae    | whole plants        | [111]      |
| 105 | Selaginella moellendorfii | Selaginellaceae | whole plants        | [112]      |
| 106 | Selaginella niponica | Selaginellaceae   | leaves              | [1]        |
| 107 | Selaginella nothohybrida | Selaginellaceae  | whole plants        | [113]      |
| 108 | Selaginella pachystachys | Selaginellaceae | leaves              | [1]        |
| 109 | Selaginella puvinata | Selaginellaceae    | -                   | [114]      |
| 110 | Selaginella remotifolia | Selaginellaceae  | -                   | [115]      |
| 111 | Selaginella rupestris | Selaginellaceae    | whole plants        | [116]      |
| 112 | Selaginella sanguinolenta | Selaginellaceae | -                   | [117]      |
| 113 | Selaginella selaginoides | Selaginellaceae | whole plants        | [118]      |
| 114 | Selaginella sinensis | Selaginellaceae     | herbs               | [119]      |
| 115 | Selaginella stauntoniana | Selaginellaceae | whole plants        | [120]      |
| 116 | Selaginella tamariscina | Selaginellaceae    | leaves              | [1]        |
| 117 | Selaginella uncinata | Selaginellaceae     | herbs               | [121]      |
| 118 | Selaginella wildenovii | Selaginellaceae  | leaves              | [122]      |
| 119 | Speranskiia Tuberculata | Euphorbiaceae  | aerial parts         | [123]      |
| 120 | Struthiola argenta | Thymelaeaceae        | whole plants        | [124]      |
| 121 | Taxus baccata     | Taxaceae             | needles             | [125]      |
| 122 | Thuja orientalis  | Cupressaceae         | leaves              | [126]      |
| 123 | Tmesipteris tannensis | Psilotaceae         | -                   | [127]      |
| 124 | Torreya nucifera  | Taxaceae             | leaves              | [128]      |
| 125 | Torreya yunnanensis | Taxaceae            | leaves, twigs       | [129]      |
| 126 | Viburnum chinshanense | Caprifoliaceae   | aerial parts         | [130]      |
| 127 | Zabelia taybiyounii | Caprifoliaceae      | leaves              | [131]      |

>: not mentioned.

3. Extraction and Isolation

To obtain amentoflavone from plants as much as possible, and to fully utilize these plant sources, some studies have been carried out to optimize the extraction technology. A central composite design (CCD) method was used to optimize the extraction technology of amentoflavone from *Taxus chinensis* by supercritical-CO$_2$ fluid extraction (SFE-CO$_2$) with methanol as a co-solvent. The highest yield reached 4.47 mg/g when the plant was extracted with 78.5% ethanol at 48 °C under a pressure
of 25 Mpa for 2.02 h [135]. With 35% water in ChCl/1,4-butanediol (1:5) as the extraction solvent, 0.518 mg/g of amentoflavone could be extracted from Chamaecyparis obtusa leaves at 70 °C for 40 min with a solid/liquid ratio of 0.1 g/mL, which was optimized by a response surface methodology [136].

Like other phytochemicals, separation and isolation of amentoflavone were mainly performed with conventional thin layer chromatography [23,24] and column chromatography, in which silica gel [15,18,25], polyamide [16], macroporous adsorption resin [85,86], octadecyl silane [11,22], middle chromatogram isolation (MCI) gel [51], and gel (Sephadex LH-20) [12,13,27] were used as stationary phases. In most cases, some of the above methods were combined for use [51,63,82,88,115,137]. Additionally, as a novel isolation method, high-speed counter-current chromatography (HSCCC) has been widely used to isolate this bioflavonoid. A preparative isolation method with HSCCC was adopted to isolate amentoflavone from Selaginella doederleinii. The mixed solvent consisting of n-hexane:ethyl acetate:methanol:water (1:2:1.5:1.5, v/v/v/v) was employed for HSGCC of ethyl acetate extract of this plant. As a result, with an approximate yield of 0.34 mg from 1 g of crude plant, amentoflavone of 91.4% purity was obtained [138]. In another experiment, with HSCCC and n-hexane:ethyl acetate:methanol:water (2.2:2.8:2:3, v/v/v), 65.31 mg amentoflavone (98% purity) was isolated from approximately 2.5 g of Selaginella tamariscina [139].

4. Natural Derivatives

There are also a large number of derivatives with different substitution positions and types in the natural plants (Figure 2). In most cases, they exist in the same plant with amentoflavone. Amentoflavone is considered as a dimer of two apigenins with six hydroxyl groups on the positions of C5, C7, C4′, C5″, C7″, and C4″ in its structure (Figure 1). Among these groups the C7-, C4′-, C7″-, or C4″-hydroxyl group is easily substituted by a methoxyl group. 7-O-methylamentoflavone (sequoiaflavone), 4′-O-methylamentoflavone (bilobetin), 7″-O-methylamentoflavone (sotetsuflavone), and 4″-O-methylamentoflavone (podocarpusflavone A) are the natural derivatives with a single methoxyl group. There are five derivatives with two methoxyl groups isolated in the plants, i.e., 7,4″-di-O-methylamentoflavone (podocarpusflavone B), 4′,4″-di-O-methylamentoflavone (isoginkgetin), 7,4′-di-O-methylamentoflavone (ginkgetin), 7,7″-di-O-methylamentoflavone, and 4′,7″-tri-O-methylamentoflavone. 7,4′,4″-tri-O-methylamentoflavone (sciadopitysin), 7,7″,4″-tri-O-methylamentoflavone (heveaflavone), and 4′,7″,4″-tri-O-methylamentoflavone (kayaflavone) are the derivatives with three methoxyl groups. Furthermore, 7,4′,7″,4″-tetra-O-methylamentoflavone has also been found in some plants. Additionally, there are some other derivatives, such as 6-methy-7,4′-di-O-methylamentoflavone (taiwanhomoflavone A), 6″-O-hydroxyamentoflavone (sumaflavone), 3″″-O-methylamentoflavone, 5′-hydroxyamentoflavone, and some glycosides. All of the compounds above and their plant sources are listed in Table 2.

In the structure of amentoflavone, carbon-carbon double bonds of C2-C3 and C2″-C3″ are easily hydrogenated, too. In a large number of plants, the hydrogenation products present include (2S)-2,3-dihydroamentoflavone, (2′S)-2″,3″-dihydroamentoflavone, and (2S,2′S)-2,3,2″,3″-tetrahydroamentoflavone, along with their C4′-O-methyl derivatives, such as (2S)-2,3-dihydro-4′-O-methylamentoflavone, (2′S)-2″,3″-dihydro-4′-O-methylamentoflavone, (2S,2′S)-2,3,2″,3″-tetrahydro-4′-O-methylamentoflavone, and their glycosides (Table 3).
Figure 2. Chemical structures of natural derivatives of amentoflavone in plants.
Table 2. Substituted derivatives of amentoflavone.

| No. | Compounds                                                                 | Sources                                                                 |
|-----|---------------------------------------------------------------------------|------------------------------------------------------------------------|
| 1   | Bilobetin                                                                 | Celaenodendron mexicanum [45], Cephalotaxus koreana [47], Chamaecyparis obtusa [49], Cyclobalana japonica var. wilsonii [103], Selaginella uncinata [137], Selaginella willdenowii [124], Taxus baccata [127], Torreya nuclifera [131] |
| 2   | Podocarpsflavone A                                                        | Allamanda monticola [15], Antidesma bunius [17], Caesalpinia pyramidalis [23], Celaenodendron mexicanum [144], Chamaecyparis obtusa [49], Cuscuta japonica [97], Cuscuta revoluta [56], Dacrydium araucarioides [6], Dacrydium cupressinum [146], Microbiota decussata [90], Selaginella bryophyta [106,141], Selaginella moellendorfii [142,143], Taxus baccata [127] |
| 3   | sequoiaflavone                                                            | Amanoa almerinidae [11], Amentotaxus yunnanensis [132], Androunce aublettii [16], Campylobacter caldihum [38], Chamaecyparis obtusa [49], Cupressaceae [84], Dacrydium araucarioides [6], Dacrydium cupressinum [146], Elateriospermum tapos [146], Microbiota decussata [90], Selaginella bryophyta [106,141], Selaginella moellendorfii [142,143], Taxus baccata [127] |
| 4   | Sotetsuflavone                                                            | Amanoa almerinidae [11], Amentotaxus yunnanensis [132], Androunce aublettii [16], Campylobacter caldihum [38], Chamaecyparis obtusa [49], Cupressaceae [84], Dacrydium araucarioides [6], Dacrydium cupressinum [146], Elateriospermum tapos [146], Microbiota decussata [90], Selaginella bryophyta [106,141], Selaginella moellendorfii [142,143], Taxus baccata [127] |
| 5   | Ginkgetin                                                                 | Celaenodendron mexicanum [45], Cephalotaxus koreana [47], Chamaecyparis obtusa [49], Dacrydium araucarioides [6], Elateriospermum tapos [146], Microbiota decussata [90], Selaginella bryophyta [106,141], Selaginella moellendorfii [142,143], Selaginella ruiziana [109,138,149], Selaginella uncinata [137], Selaginella willdenowii [124], Taxus baccata [127] |
| 6   | Isoginkgetin                                                              | Chamaecyparis obtusa [49], Cyclobalana japonica var. wilsonii [103], Cyclobalana japonica var. wilsonii [103], Selaginella uncinata [137], Selaginella willdenowii [124] |
| 7   | Podocarpsflavone B                                                        | Amanoa almerinidae [11], Chamaecyparis obtusa [49], Cyclobalana japonica var. wilsonii [103], Selaginella uncinata [137], Selaginella willdenowii [124] |
| 8   | 4',5',6-tri-O-methylamentoflavone                                         | Cephalotaxus fortunei [46], Cephalotaxus koreana [47], Cephalotaxus oliveri [48], Chamaecyparis obtusa [49], Cunninghamia lanceolata [51], Dacrydium araucarioides [6], Cyclobalana japonica var. wilsonii [103], Elateriospermum tapos [146], Microbiota decussata [90], Selaginella bryophyta [106,141], Selaginella moellendorfii [142,143], Taxus baccata [127], Taxus maudiae [150], Torreya nuclifera [131], Torreya yunnanensis [132] |
| 9   | 7,7',8-tri-O-methylamentoflavone                                         | Amentogetaxus yunnanensis [132], Chamaecyparis obtusa [49], Dacrydium araucarioides [6], Dacrydium cupressinum [146], Elateriospermum tapos [146], Selaginella uncinata [137], Selaginella willdenowii [124] |
| 10  | Heveaflavone                                                             | Dacrydium araucarioides [6], Dacrydium cupressinum [146], Elateriospermum tapos [146], Podocarpus brevifolius [99], Podocarpus henkelii [151], Ranunculus ternatus [99], Selaginella bryophyta [106,141], Selaginella moellendorfii [142,143], Taxus baccata [127] |
| 11  | kayaflavone                                                               | Ranunculus ternatus [99], Selaginella moellendorfii [112] |
| 12  | Sciadopitysin                                                             | Cephalotaxus fortunei [46], Cephalotaxus koreana [47], Cephalotaxus oliveri [48], Chamaecyparis obtusa [49], Cunninghamia lanceolata [51], Dacrydium araucarioides [6], Cyclobalana japonica var. wilsonii [103], Elateriospermum tapos [146], Microbiota decussata [90], Selaginella bryophyta [106,141], Selaginella moellendorfii [142,143], Taxus baccata [127], Taxus maudiae [150], Torreya nuclifera [131], Torreya yunnanensis [132] |
| 13  | 7,4',5'-tri-O-methylamentoflavone                                         | Dacrydium araucarioides [6], Dacrydium cupressinum [146], Elateriospermum tapos [146], Podocarpus brevifolius [99], Podocarpus henkelii [151], Podocarpus nagi [152], Retrophyllum rosipilosii [100], Selaginella denticulata [108], Selaginella moellendorfii [112], Taxus baccata [153], Wollemia nobilis [154] |
| 14  | 7,4',5',6'-tetra-O-methylamentoflavone                                   | Cephalotaxus fortunei [46], Dacrydium pteric [146], Dacrydium rospigliosii [145], Podocarpus brevifolius [145], Podocarpus henkelii [151], Podocarpus nagi [152], Retrophyllum rosipilosii [100], Selaginella denticulata [108], Selaginella moellendorfii [112], Taxus baccata [153], Wollemia nobilis [154] |
| 15  | 7,4',5',6'-penta-O-methylamentoflavone                                   | Cephalotaxus fortunei [46], Dacrydium pteric [146], Dacrydium rospigliosii [145], Podocarpus brevifolius [145], Podocarpus henkelii [151], Podocarpus nagi [152], Retrophyllum rosipilosii [100], Selaginella denticulata [108], Selaginella moellendorfii [112], Taxus baccata [153], Wollemia nobilis [154] |
| 16  | 3',5'-O-methylamentoflavone                                              | Lonicera macranthoides [84] |
| 17  | 6'-2-hydroxy-3-methyl-3-butenyl-amentoflavone                            | Calophyllum venulosa [37], Garcinia bakeriana [66] |
### Table 2. Cont.

| No. | Compounds | Sources |
|-----|-----------|---------|
| 18  | 6’-(3-methyl-2-butenyl)-amentoflavone | Calophyllum venulosum [37] |
| 19  | Garciniaflavone A | Garcinia subelliptica [73] |
| 20  | Garciniaflavone B | Garcinia subelliptica [73] |
| 21  | Garciniaflavone C | Garcinia subelliptica [73] |
| 22  | Garciniaflavone D | Garcinia subelliptica [73] |
| 23  | 3’β’-biisokaempferide | Nanuza plicata [92] |
| 24  | 5’-hydroxyamentoflavone | Caesalpinia pyramidalis [23] |
| 25  | Sumaflavone | Selaginella tamariscina [155,156] |
| 26  | Pyranoamentoflavone | Calophyllum inophylloide [30], Calophyllum venulosum [37] |
| 27  | 7,4’′-di-O-methylpyranoamentoflavone | Calophyllum venulosum [37] |
| 28  | 7,4’′′-di-O-methylpyranoamentoflavone | Calophyllum venulosum [37] |
| 29  | Amentoflavone-7,4’′-tri-O-β-D-glucopyranoside | Psilotum nudum [157] |
| 30  | Amentoflavone-4’′-di-O-β-D-glucopyranoside | Psilotum nudum [157] |
| 31  | Amentoflavone-7,4’′′-di-O-β-D-glucopyranoside | Psilotum nudum [157] |
| 32  | Taiwanhomoflavone A | Cephalotaxus wilsoniana [158] |

### Table 3. Hydrogenation derivatives of amentoflavone.

| No. | Compounds | Sources |
|-----|-----------|---------|
| 33  | (2S)-2,3-dihydro-7-O-β-D-glucopyranosylamentoflavone | Cycas revoluta [159] |
| 34  | (2S)-2,3-dihydro-7,7′-di-O-β-D-glucopyranosylamentoflavone | Cycas revoluta [159] |
| 35  | (2S,2′)-2,3′,3′-dihydro-4′-O-methylamentoflavone | Selaginella remotifolia [115], Selaginella uncinata [123,126] |
| 36  | (2S,2′)-2,3′-dihydro-4′-O-methylamentoflavone | Cycas circinalis [56], Selaginella remotifolia [115], Selaginella uncinata [123,127] |
| 37  | (2S,2′)-2,3′,3′-dihydro-4′-O-methylamentoflavone | Cycas circinalis [56], Selaginella uncinata [123] |
| 38  | (2S,2′)-2,3′,3′-dihydro-4′-O-methylamentoflavone | Cycas beddomei [55,161], Cycas revoluta [56], Dysoxylum cauliflorum [162], Selaginella brauertis [106,141], Selaginella uncinata [123] |
| 39  | (2S,2′)-2,3′,3′-dihydro-4′-O-methylamentoflavone | Calophyllum venulosum [37], Cycas beddomei [55,161], Cycas pectinata [58], Cycas revoluta [56], Selaginella brauertis [106,141], Selaginella mollendoftii [142], Selaginella remotifolia [115], Selaginella tamariscina [163], Selaginella uncinata [123,127] |
| 40  | (2S,2′)-2,3′-dihydro-4′-O-methylamentoflavone | Selaginella brauertis [106,141], Selaginella remotifolia [115], Selaginella tamariscina [163], Selaginella uncinata [123] |
| 41  | (2S,2′,3′)-2,3′,3′-tetrahydroisoginkgetin | Cycas circinalis [56] |
| 42  | (2S,2′,3′)-2,3′,3′-tetrahydroisoginkgetin | Cycas circinalis [56] |
| 43  | (2S,2′)-2,3′-dihydro-4′-O-methylamentoflavone | Selaginella remotifolia [115] |
| 44  | (2S,2′)-2,3′-dihydro-7,7′-di-O-methylamentoflavone | Amentotaxus yunnanensis [132] |
| 45  | (2S,2′)-2,3′-dihydro-4′-O-methylamentoflavone | Cycas beddomei [55,161] |
5. Pharmacology

As a ubiquitous biflavonoid, amentoflavone has been found with a large number of pharmacological functions, such as anti-inflammation, anti-oxidation, anti-tumor, anti-senescence, anti-virus, anti-diabetes, neuroprotective activities, and effects on cardiovascular system and central nervous system.

5.1. Anti-Inflammation and Anti-Oxidation

Oxidative stress response is one part of inflammatory response. Amentoflavone, isolated from *Garcinia brasiliensis*, exhibited inhibitory effects on the productions of superoxide anion and total reactive oxygen species (ROS) in phorbol 12-myristate 13-acetate-stimulated human neutrophils. In human erythrocytes induced by 2,2′-azobis(2-amidinopropane) hydrochloride, it also inhibited the oxidant hemolysis and lipid peroxidation [2].

In rat astrocytoma cell line, lipopolysaccharide (LPS) could increase NO, ROS, malondialdehyde (MDA), and decrease reduced-glutathione (GSH), while tumor necrosis factor-α (TNF-α) was increased by LPS in a human monocytic leukemia cell line. All of the changes above were attenuated by amentoflavone significantly. However, there were no notable effects on the cells [164]. In RAW 264.7 cells stimulated with LPS, amentoflavone was observed to suppress the production of NO, prostaglandin E-2 (PGE-2), and the nuclear translocation of c-Fos, a subunit of activator protein (AP)-1. Additionally, extracellular signal-regulated kinase (ERK), which mediated c-Fos translocation, was inhibited by the active biflavonoid [165]. In the supernatant media of human peripheral blood mononuclear cells (PBMCs), amentoflavone could inhibit the increases of interleukin-1β (IL-1β), IL-6, TNF-α, and PGE2 induced by phytohaemagglutinin (PHA) [3].

The IC$_{50}$ values of amentoflavone were 31.85 ± 4.75, 198.75 ± 33.53, 147.14 ± 10.52, 93.75 ± 16.36, 167.69 ± 13.90, and 137.95 ± 18.66 µM, respectively, for DNA, cytosine, uracil, adenine, thymine, guanine, and deoxyribose damage. Radical-scavenging assays indicated that amentoflavone could effectively scavenge center dot O$_{2}^{-}$, DPPH, ABTS$^+$ radicals with IC$_{50}$ values of 8.98 ± 0.23, 432.25 ± 84.05, 7.25 ± 0.35 µM, respectively [166].

5.2. Anti-Tumor

Amentoflavone exerted good cytotoxic effect on cervical adenocarcinoma (HeLa) cells with IC$_{50}$ values of 20.7 µM [5].

After breast cancer MCF-7 cells were treated with amentoflavone, there were some cellular changes, including DNA and nuclear fragmentation, and down-regulation of calcium and intracellular reactive oxygen species. Additionally, some marks of mitochondrial-mediated apoptosis were observed, such as the activation of caspase 3, the reduction of mitochondrial inner-membrane potential, and the release of cytochrome c from mitochondria [167].

Amentoflavone also could significantly inhibit solid tumor development that was induced by B16F-10 melanoma in C57BL/6 mice. The mechanism might be related to inhibiting cell progression from G0/G1 to S phase and to regulating genes which were involved in cell cycle and apoptosis, such as P21, P27, Bax, caspase-9, etc. [168].

Recently, fatty acid synthase (FASN) has been considered as a potential target to treat cancer. Some studies indicated that amentoflavone could inhibit FASN expression in human epidermal growth factor receptor 2 (HER2)-positive human breast carcinoma SKBR3 cells. The inhibition decreased the translocation of sterol regulatory element-binding protein 1 (SREBP-1) in SKBR3 cells. The biflavonoid was also found to down-regulate HER2 protein and mRNA, to up-regulate polyoma enhancer activator 3 (PEA3), a transcriptional repressor of HER2 and to inhibit phosphorylation of protein kinase B (PKB), mechanistic target of rapamycin (mTOR) and c-Jun N-terminal kinases (c-NK) [169]. In another experiment, amentoflavone was observed to increase the cleavage-activity of caspase-3, to suppress SKBR3 cell activity, and to have no effect on FASN-nonexpressed NIH-3T3 normal cell growth [170].
5.3. Anti-Senescence

Ultraviolet B (UVB) irradiation was found to increase the levels of Lamin A and phospho-H2AX protein in normal human fibroblasts. These cases were present in premature aging diseases or normally old individuals. An investigation indicated amentoflavone was able to ameliorate these damages and to protect nuclear aberration significantly, which showed the anti-senescence activity for some skin aging processes related with UVB [4]. Another investigation in UVB-induced normal human fibroblasts found that amentoflavone could inhibit the activation of ERK without affecting ERK protein level, p38, and JNK activation. In addition, the biflavonoid could decrease phospho-c-Jun and c-Fos protein expressions, which were AP-1 transcription factor components. The findings suggested the potential of amentoflavone to prevent or treat skin photoaging [171].

5.4. Anti-Diabetes

Amentoflavone was observed to ameliorate glucose disorder, regulate insulin secretion, and restore the pancreas in streptozotocin-induced diabetic mice and the optimum dose was 60 mg/kg [172]. In another anti-diabetes study, this active biflavonoid showed its activities against \( \alpha \)-glucosidase (IC\(_{50} \) 8.09 ± 0.023 \( \mu \)M) and \( \alpha \)-amylase (IC\(_{50} \) 73.6 ± 0.48 \( \mu \)M) [58].

Inhibition of protein tyrosine phosphatase 1B (PTP1B) has been considered as a strategy to treat type 2 diabetes. Amentoflavone was screened to inhibit PTP1B with IC\(_{50} \) value of 7.3 ± 0.5 \( \mu \)M and proved to be a non-competitive inhibitor of PTP1B by kinetic study. There was a dose-dependent increase in tyrosine phosphorylation of insulin receptor (IR) after 32D cells with overexpression of IR were treated with amentoflavone [173].

5.5. Anti-Virus

Amentoflavone exhibited its anti-dengue potential in a screening experiment, which may be mediated by inhibiting Dengue virus NS5 RNA-dependent RNA polymerase [6]. Among the isolated twelve components from Torreya nucifera with a bioactivity guide, amentoflavone was proved as the most active one to inhibit severe acute respiratory syndrome coronavirus (SARS-CoA) with IC\(_{50} \) value of 8.3 \( \mu \)M. The effect was concluded relative to the inhibition of chymotrypsin-like protease (3CL\(_{\text{pro}} \)) [131]. Amentoflavone was also found to decrease Coxackievirus B3 (CVB3) replication by inhibiting fatty acid synthase (FAS) expression [174]. Moreover, in cases of human immunodeficiency virus (HIV) and respiratory syncytial virus (RSV), amentoflavone showed good performance with IC\(_{50} \) values of 119 \( \mu \)M [102] and 5.5 \( \mu \)g/mL [120], respectively.

5.6. Effects on Central Nervous System

After amentoflavone was isolated from Cnestis ferruginea, Ishola et al. carried out some investigations about its effects on central nervous system. In one pharmacological investigation, oral administration of amentoflavone was proved to attenuate depression induced by metergoline (5-HT2 receptor antagonist), prazosin (\( \alpha1 \)-adrenoceptor antagonist), or yohimbine (\( \alpha2 \)-adrenoceptor antagonist), and to ameliorate anxiety stimulated by flumazenil (ionotropic GABA receptor antagonist). These findings suggested that the active biflavonoid showed the antidepressant and anxiolytic effects through interactions with the receptors above [175]. In another study, it was found that the naturally-occurring biflavonoid could prevent scopolamine-induced memory impairment, inhibit AChE and enhance antioxidant enzyme activity in mice, which exhibited its protection against memory deficits [176].

In glutamate injured HT22 hippocampal cells, amentoflavone showed neuroprotective activity. The active compound was able to restore the reduced superoxide dismutase (SOD) activity, glutathione reductase (GR) activity and glutathione content induced by glutamate. Additionally, it was found to prevent the phosphorylation of ERK1/2 [177]. Amentoflavone also exerted neuroprotective activity in pilocarpine-induced epileptic mice. After preventive administration of the biflavonoid for three
consecutive days, the model mice showed some signs of improvement, including reduction of epileptic seizures, shortened attack time, reduction in hippocampal neuron loss and apoptosis, and suppressed nuclear factor-kappa B (NF-κB) activation and expression [8].

5.7. Effects on the Cardiovascular System

Amentoflavone was tested to have a vasorelaxant effect on thoracic aortic blood vessels of rats in vitro, which was concluded as being endothelium-dependent and involved with NO [178].

Amentoflavone also had a protective effect on vascular endothelial cells. The viability of human umbilical vein endothelial cells (HUVECs) was promoted and the ratio of cells at S phase was increased by treatment with this biflavonoid [179]. Some results of cell studies indicated that amentoflavone could increase the NO content, decrease the levels of VCAM-1, E-selectin, IL-6, IL-8, and ET-1, enhance SOD activity, reduce MDA content, downregulate the protein expressions of VCAM-1, E-selectin, and NF-κB p65, up-regulate IκBα, and attenuate the NF-κB p65 transfer to the cell nucleus, which proved its protection on vascular endothelial cells [9].

Cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE) inhibitor has been found to inhibit the activity of cAMP-PDE-3 in myocardial cells and vascular smooth muscle cells, which could enhance myocardial contraction, expand peripheral vessels, and improve hemodynamics of heart failure patients. Amentoflavone showed a potent inhibitory function on cAMP-PDE [180]. The effect study of amentoflavone on isolated rat heart exhibited that the phytochemical significantly increased the beat rate at dosage of 10–50 µg/mL [181].

5.8. Antifungal Activity

Amentoflavone was investigated to have antifungal activity against several pathogenic fungal strains, including Candida albicans, Saccharomyces cerevisiae, and Trichosporon beigelii. In Candida albicans, it could stimulate the intracellular trehalose accumulation and disrupt the dimorphic transition, which meant a stress response to the component [182]. Further research on its antifungal mechanism of Candida albicans suggested that this active phytochemical arrested cell cycles during the S-phase and inhibited cell proliferation and division [183]. The anti-candida activity was proved to be related to apoptotic cell death, which may be associated with the mitochondrial dysfunction. Additionally, hydroxyl radicals induced by amentoflavone may play a significant role in apoptosis [7].

5.9. Other Bioactivities

In addition to the pharmacological functions above, significant evidence showed its other bioactivities (Table 4), such as anti-hyperlipidemia [184], anti-hypertrophic scar [185], anti-psoriasis [186], anti-ulcerative colitis [187], hepatoprotection [184], osteogenesis effect [188] and radioprotection [189].
### Table 4. Other pharmacological effects of amentoflavone.

| Function                  | Inducer          | Model                        | Efficacy Evaluation                                                                                           | Reference |
|---------------------------|------------------|------------------------------|---------------------------------------------------------------------------------------------------------------|-----------|
| Anti-hyperlipidemia       | High-cholesterol diet | Male Kunming mice            | Decreased TG, TC, LDL-C in serum                                                                                  | [184]     |
|                           |                   |                              | Increased HDL-C                                                                                               |           |
| Anti-hypertrophic scar    | -                | HSFBs                        | Inhibited cell viability, induced apoptosis Regulated Bax, TCTP, caspase-3, caspase-8, caspase-9               | [185]     |
|                           |                   | SVECs                        | Inhibited cell viability                                                                                      |           |
|                           |                   |                              | Inhibited migration, invasion, tubular structure formation                                                    |           |
| Anti-psoriasis            | Imiquimod        | Male BALBc Mice              | Reduced skinfold thickening Improved erythema and scaling scores, histological lesions Suppressed increases of TNF-α, IL-17A, IL-22, IL-23 | [186]     |
|                           | M5 cocktail *    | Human keratinocytes          | Inhibited cell proliferation, promoted apoptosis Decreased overexpression of cyclin D1, cyclin E, IL-17A, IL-22 Inhibited the up-regulation of p65 NF-κB |           |
| Anti-ulcerative colitis   | Acetic acid      | Male Wistar rats             | Decreased mucosal injury score, vascular permeability Diminished LDH and MPO activity Increased GSH, SOD; decreased LPO, NO Reduced the colonic TNF-α, IL-1β, IL-6 Inhibited expression of inOS and COX-2 Inhibited activation and translocation of NF-κB (p65/p50) | [187]     |
| Hepatoprotection          | CCl4             | Male Kunming mice            | Decreased GOT, GPT, hepatic MDA Increased hepatic SOD                                                          | [184]     |
|                           |                   |                              |                                                                                                               |           |
| Osteogenesis effect       | -                | Human mesenchymal stem cells | Enhanced proliferation, ALP activity, mineralization Uregulated expression of RUNX2, osterix proteins Increased the levels of phosphorylated JNK and p-p38 | [188]     |
| Radioprotection           | Co-60 irradiation | V79 Chinese hamster lung fibroblast cells | Inhibited apoptosis, promoted the G2 phase Decreased the concentration of ROS and mitochondrial mass | [189]     |

ALP: alkaline phosphatase; COX-2: cyclooxygenase-2; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; HDL-C: high-density lipoprotein cholesterol; HSFBs: hypertrophic scar fibroblasts; iNOS: inducible nitric oxide synthase; LDH: lactate dehydrogenase; LDL-C: low-density lipoprotein cholesterol; RUNX2: runt-related transcription factor 2; SVECs: Simian virus-40-transformed murine endothelial cells; TC: total cholesterol; TCTP: translationally controlled tumour protein; TG: triglyceride; -: no inducer; *: IL-1α, IL-17A, IL-22, Oncostatin M, and TNF-α, each at 10 ng/mL for two days.
6. Pharmacokinetics

In recent years, pharmacokinetic studies of extracts and bioactive compounds from traditional Chinese medicine and natural medicine have become research highlights. As a representative biflavonoid with several pharmacological functions, amentoflavone was not an exception.

In a pharmacokinetic investigation, amentoflavone was administrated to rats with different types including oral gavage (po, 300 mg/kg), intravenous (iv, 10 mg/kg) and intraperitoneal (ip, 10 mg/kg) injection. As a result, 90.7% of the total amentoflavone was discovered to circulate as conjugated metabolites after po administration. In the plasma of rats with iv and ip injection, 73.2% ± 6.29% and 70.2% ± 5.18% of the total amentoflavone was present as conjugated metabolites. In addition, the bioavailability of this compound with po administration was 0.04% ± 0.01%, much lower than that with ip injection (77.4% ± 28.0%) [190].

Pharmacokinetic characteristic of amentoflavone individually or together with other components in normal rats and hyperlipidemic model rats have been studied and compared [191]. In the case of oral administration of only this biflavonoid, $T_{1/2}$ and $T_{max}$ of amentoflavone were determined as 2.06 h ± 0.13 h, 1.13 h ± 0.44 h in normal rats and 1.91 h ± 0.32 h, 0.96 h ± 0.10 h in model rats, respectively. Shixiao San is a famous TCM formula containing amentoflavone [192]. After oral administration of a Shixiao San decoction, $T_{1/2}$ and $T_{max}$ of amentoflavone were determined as 3.34 h ± 0.37 h, 4.00 h ± 0.00 h in normal rats, and 4.19 h ± 0.64 h, 4.17 h ± 0.40 h in model rats.

7. Conclusions and Future Perspectives

From the contents above, we could conclude that amentoflavone is a bioactive biflavonoid with a variety of pharmacological effects, which has been derived from many natural plants.

Emerging pharmacological evidence has proved the effects of amentoflavone on various aspects, including anti-inflammation, anti-oxidation, anti-diabetes, anti-senescence, anti-virus, anti-tumor activities, and effects on the central nervous system and cardiovascular system. However, the majority of these bioactivity data came from studies involved with cells in vitro, while the number of studies with model animals in vivo was very low. As we know, bioactivity in vitro is unable to represent and explain biological effect in vivo, while pharmacological investigations in model animals are indispensable prior to clinical use. Thus, some bioactivities in vitro should be confirmed and proved by integral animal experiments in the future. In terms of present pharmacokinetic study, the findings have suggested that amentoflavone metabolism procedure was very rapid and there was also a very low bioavailability after oral administration of this biflavonoid in rats. This may be one reason why fewer animal model experiments have been performed. We speculate that improving the bioavailability with introduction of structural modification, precursor synthesis, or particular pharmaceutical necessities may be one focus of amentoflavone studies. Meanwhile, since there are some differences of pharmacokinetics between normal and model animals, concerning the specific pharmacological effects, the pharmacokinetic investigations on corresponding model animals should also be carried out.

Amentoflavone has been found, isolated, and identified in over 120 natural plants, which exhibited its rich plant source. The content of any phytochemical varies very much in different species or in different regions. Among 11 plants from Selaginella species, the biflavonoid was found with the high contents between 1.0% and 1.1% in Selaginella sinensis, Selaginella davidii, and Selaginella mollendorfii from some specific production areas, while the contents were no more than 1.0% in the rest, and even below 0.1% in some [193,194]. It is well-known that extraction yield will be lower than the determined content. In addition, most of the sources are perennial plants and their recovery or reproduction will last not a short time. Thus, at present, plant-derived preparation seems to cost too much. This may be another reason of fewer animal model experiments, which would need much higher amounts of the biflavonoid than cell experiments. We must find some solutions to get the sufficient quantity for studies in the future, such as looking for other plants with much higher contents, biological synthesis, and even chemical synthesis.
Taken together, since amentoflavone is a promising and naturally-occurring biflavonoid with so many bioactivities, its systematic druggability research as a candidate drug is obviously necessary, including its preparation study (extraction and isolation from plants, chemical synthesis, or biological synthesis), structural modification study, Absorption-Distribution-Metabolism-Excretion (ADME) study in normal animals and animal models, acute and chronic toxicological studies. Thus, we can make full use of amentoflavone as a drug and employ it in the prevention and treatment of diseases.

In summary, this paper has provided a full-scale profile of amentoflavone on its plant sources, natural derivatives, pharmacology, and pharmacokinetics, and also proposed some issues and perspectives which may be of concern in the future. We believe this literature review will help us more comprehensively understand, and take advantage more fully, the naturally-occurring biflavonoid amentoflavone.

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References

1. Okigawa, M.; Hwa, C.W.; Kawano, N.; Rahman, W. Biflavones in Selaginella species. *Phytochemistry* **1971**, *10*, 3286–3287. [CrossRef]
2. Arwa, P.S.; Zeraik, M.L.; Ximenes, V.F.; da Fonseca, L.M.; Bolzani, V.S.; Silva, D.H.S. Redox-active biflavonoids from *Garcinia brasiliensis* as inhibitors of neutrophil oxidative burst and human erythrocyte membrane damage. *J. Ethnopharmacol.* **2015**, *174*, 410–418. [CrossRef] [PubMed]
3. Abdallah, H.M.; Almowallad, F.M.; Esmat, A.; Shehata, I.A.; Abdel-Sattar, E.A. Anti-inflammatory activity of flavonoids from *Chrozophora tinctoria*. *Phytochem. Lett.* **2015**, *13*, 74–80. [CrossRef]
4. Park, N.H.; Lee, C.W.; Bae, J.H.; Na, Y.J. Protective effects of amentoflavone on Lamin A-dependent UVB-induced nuclear aberration in normal human fibroblasts. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6482–6484. [CrossRef] [PubMed]
5. Ndongo, J.T.; Issa, M.E.; Messi, A.N.; Mbeng, J.N.; Cuenet, M.; Pegnyemb, D.E.; Bochet, C.G. Cytotoxic flavonoids and other constituents from the stem bark of *Ochna schweinfurthiana*. *Nat. Prod. Res.* **2015**, *29*, 1684–1687. [CrossRef] [PubMed]
6. Coulerie, P.; Nour, M.; Maciuk, A.; Eydoux, C.; Guillemot, J.C.; Lebouvier, N.; Hnawia, E.; Leblanc, K.; Lewin, G.; Canard, B.; et al. Structure-activity relationship study of biflavonoids on the Dengue virus polymerase DENV-NS5 RdRp. *Planta Med.* **2013**, *79*, 1313–1318. [CrossRef] [PubMed]
7. Hwang, I.S.; Lee, J.; Jin, H.G.; Woo, E.R.; Lee, D.G. Amentoflavone stimulates mitochondrial dysfunction and induces apoptotic cell death in *Candida albicans*. *Mycopathologia* **2012**, *173*, 207–218. [CrossRef] [PubMed]
8. Zhang, Z.; Sun, T.; Niu, J.G.; He, Z.Q.; Liu, Y.; Wang, F. Amentoflavone protects hippocampal neurons: Anti-inflammatory, antioxidative, and antiapoptotic effects. *Neural Regen. Res.* **2015**, *10*, 1125–1133. [PubMed]
9. Zheng, X.K.; Liu, C.X.; Zhai, Y.Y.; Li, L.L.; Wang, X.L.; Feng, W.S. Protection effect of amentoflavone in *Selaginella tamariscina* against TNF-α-induced vascular injure of endothelial cells. *Acta Pharm. Sin.* **2013**, *48*, 1503–1509.
10. Chinese Pharmacopeia Commission. *Pharmacopoeia of the People’s Republic of China*; Chinese Medical Science Press: Beijing, China, 2015; Volume 1, pp. 226–227.
11. Leong, K.I.; Alvarez, P.F.; Compagnone, R.S.; Suarez, A.I. Isolation and structural elucidation of chemical constituents of *Amanoa almerindae*. *Pharm. Biol.* **2009**, *47*, 496–499. [CrossRef]
12. Calvo, T.R.; Lima, Z.P.; Silva, J.S.; Ballesteros, K.V.; Pellizzon, C.H.; Hiruma-Lima, C.A.; Tamashiro, J.; Brito, A.R.; Takahira, R.K.; Vilegas, W. Constituents and antiulcer effect of Alchornea glandulosa: Activation of cell proliferation in gastric mucosa during the healing process. *Biol. Pharm. Bull.* 2007, 30, 451–459. [CrossRef] [PubMed]

13. Calvo, T.R.; Demarco, D.; Santos, F.V.; Moraes, H.P.; Baua, T.M.; Varanda, E.A.; Côlus, I.M.; Vilegas, W. Phenolic compounds in leaves of *Alchornea triplinervia*: Anatomical localization, mutagenicity, and antibacterial activity. *Nat. Prod. Commun.* 2010, 5, 1225–1232. [PubMed]

14. Li, L.Z.; Wang, M.H.; Sun, J.B.; Liang, J.Y. Flavonoids and other constituents from *4-Epiisocommunic acid and amentoflavone from Caesalpinia pyramidalis* [77x357] 2010, 5, 1225–1232. [PubMed]

15. Azebaze, A.G.; Dongmo, A.B.; Meyer, M.; Ouahouo, B.M.; Valentin, A.; Nguemfo, E.L.; Nkengfack, A.E.; Ergler, W. Antimalarial and vasorelaxant constituents of the leaves of *Allanblackia monticola* (Guttiferae). *Ann. Trop. Med. Parasitol.* 2007, 101, 23–30. [CrossRef] [PubMed]

16. Wang, W.J.; Lei, J.; Xiao, Y.C.; Xi, Z.; Yu, M.; Huang, J. The separation and identiﬁcation of biflavonoids from *Androsace umbellata*. *West China J. Pharm. Sci.* 2011, 26, 420–423.

17. Trang, D.T.; Huyen, L.T.; Nghiêm, N.X.; Quang, T.H.; Hang, D.T.T.; Yen, P.H.; Tai, B.H.; Anh, H.L.T.; Binh, N.Q.; Minh, C.V.; Kiem, P.V. Tirucallane glycosides from the leaves of *Antidesma bunius* and inhibitory NO production in BV2 cells and RAW264.7 macrophages. *Nat. Prod. Commun.* 2016, 11, 935–937.

18. Tchinda, A.T.; Teshome, A.; Dagne, E.; Arnold, N.; Wessjohann, L.A. Squalene and amentoflavone from *Antidesma laciniatum*. *Bull. Chem. Soc. Ethiop.* 2006, 20, 325–328. [CrossRef]

19. Bucar, F.; Jackak, S.M.; Noreen, Y.; Kartnig, T.; Perera, P.; Bohlin, L.; Schubert-Zsilavecz, M. Amentoflavone from *Biophytum sensitivum* and its effect on COX-1/COX-2 catalysed prostaglandin biosynthesis. *Planta Med.* 1998, 64, 373–374. [CrossRef]

20. Sajjad, A.; Andrabi, S.M.A.; Qureshi, M. Flavonoids from *Biota semipervirens*. *Indian J. Heterocycl. Chem.* 2001, 11, 87.

21. Sannomiya, M.; Fonseca, V.B.; da Silva, M.A.; Rocha, L.R.M.; dos Santos, L.C.; Hiruma-Lima, C.A.; Brito, A.R.M.S.; Vilegas, W. Flavonoids and antiulcerogenic activity from *Byrsomina crassa* leaves extracts. *J. Ethnopharmacol.* 2005, 97, 1–6. [CrossRef] [PubMed]

22. Sannomiya, M.; Cardoso, C.R.; Figueiredo, M.E.; Rodrigues, C.M.; dos Santos, L.C.; dos Santos, F.V.; Serpeloni, J.M.; Côlus, I.M.; Vilegas, W.; Varanda, E.A. Mutagenic evaluation and chemical investigation of *Byrsomina intermedia* A. Juss. leaf extracts. *J. Ethnopharmacol.* 2007, 112, 319–326. [CrossRef] [PubMed]

23. Bahia, M.V.; David, J.P.; David, J.M. Occurrence of biflavones in leaves of *Caulocedrus microlepica* var. *formosana*. *Bull. Chem. Soc. Ethiop.* 2006, 20, 325–328. [CrossRef] [PubMed]

24. Prasad, J.S.; Krishnamurti, H.G. 4-Episocommunic acid and amentoflavone from *Callitris rhomboidea*. *Phytochemistry* 1977, 16, 801–803. [CrossRef]

25. Chien, S.C.; Liu, H.K.; Kuo, Y.H. Two new compounds from the leaves of *Calocedrus microlepica* var. *formosana*. *Chem. Pharm. Bull.* 2004, 52, 762–763. [CrossRef] [PubMed]

26. Da Silva, K.L.; dos Santos, A.R.S.; Mattos, P.E.O.; Yunes, R.A.; Delle-Monache, F.; Cechinel, V. Chemical composition and analgesic activity of *Calophyllum brasiliense* leaves. *Therapie* 2001, 56, 431–434. [PubMed]

27. Aminudin, N.I.; Ahmad, F.; Taher, M.; Zulkifli, R.M. Cytotoxic and antibacterial activities of constituents from *Calophyllum ferrugineum* Ridley. *Rec. Nat. Prod.* 2016, 10, 649–653.

28. Ferchichi, L.; Derbré, S.; Mahmoood, K.; Touré, K.; Guilet, D.; Litaudon, M.; Awang, K.; Hadi, A.H.; le Ray, A.M.; Richomme, P. Bioguided fractionation and isolation of natural inhibitors of advanced glycation end-products (AGEs) from *Calophyllum florationatum*. *Phytochemistry* 2012, 78, 98–106. [CrossRef] [PubMed]

29. Aminudin, N.I.; Ahmad, F.; Taher, M.; Zulkifli, R.M. Incrasammarin A-D: Four new 4-substituted coumarins from *Calophyllum incrassatum* and their biological activities. *Phytochem. Lett.* 2016, 16, 287–293. [CrossRef]

30. Goh, S.H.; Jantan, I.; Waterman, P.G. Neoflavonoid and Biflavonoid Constituents of *Calophyllum inophylloide* Ridley. *Rec. Nat. Prod.* 1992, 55, 1415–1420. [CrossRef]

31. Inuma, M.; Tosa, H.; Tanaka, T.; Ito, Y.; Yonomori, S.; Chelladurai, V.; Aquil, M.; Takahashi, Y.; Naganawa, H. Occurrence of xantholephinoids in Guttifereous plants. *Heterocycles* 1996, 43, 1521–1527. [CrossRef]

32. Chen, G.Y.; Wu, X.P.; Dai, C.Y.; Zhao, J.; Han, C.R.; Song, X.P.; Zhong, Q.X. Chemical Constituents in the Roots of *Calophyllum membranaceum* Gardn. *Acta Sci. Nat. Univ. Sunyatseni* 2009, 48, 52–56.

33. Chen, G.Y.; Han, C.R.; Song, X.P.; Huang, H.R.; Lin, Y.C. Chemical Constituents from leaves of *Calophyllum membranaceum* Gardn. *Chem. Ind. For. Prod.* 2003, 23, 73–76.
34. Alarcón, A.B.; Cuesta-Rubio, O.; Pérez, J.C.; Piccinelli, A.L.; Rastrelli, L. Constituents of the Cuban endemic species *Calophyllum pinetorum*. *J. Nat. Prod.* 2008, 71, 1283–1286. [CrossRef] [PubMed]
35. Oubada, A.; García, M.; Bello-Alarcon, A.; Cuesta-Rubio, O.; Monzote, L. Anti-leishmanial activity of leaf extract from *Calophyllum rivicule* against *Leishmania amazonensis*. *Emirates J. Food Agric.* 2014, 26, 807–812. [CrossRef]
36. Aminudin, N.I.; Ahmad, F.; Taher, M.; Zulkifi, R.M. α-Glucosidase and 15-lipoxygenase inhibitory activities of phytochemicals from *Calophyllum syringotinctum*. *Nat. Prod. Commun.* 2015, 10, 1585–1587. [PubMed]
37. Cao, S.G.; Sim, K.Y.; Goh, S.H. Biflavonoids of *Calophyllum venulosum*. *J. Nat. Prod.* 1997, 60, 1245–1250. [CrossRef]
38. Manga, S.S.E.; Tih, A.E.; Ghogomu, R.T.; Blond, A.; Bodo, B. Biflavonoid constituents of *Campylospermum* Genus (Ochnaceae). *Heli. Chin. Acta* 2013, 96, 1298–1304. [CrossRef]
39. Helene, T.; Serge, F.; Ngadjui, B.T.; Etienne, D.; Abegaz, B.M. Phenolic metabolites from the seeds of *Canarium schweinfurthii*. *Bull. Chem. Soc. Ethiop.* 2000, 14, 155–159. [CrossRef]
40. Shaari, K.; Waterman, P.G. Podophyllotoxin-type lignans as major constituents of the stems and leaves of *Casearia clareka*. *J. Nat. Prod.* 1992, 57, 720–724. [CrossRef]
41. Chen, R.; Li, Y.; Wang, X.L. Study on the chemical constituents of *Cupressus sempervirens* of *Cupressus chengiana* of phytochemicals from *Cupressocyparis leylandii*. *Chem. Ind. For. Prod.* (Lour.) Raeusch. 2007, 27, 45–48.
42. Ly, Z.C.; Yin, Y.; Lin, L.J.; Peng, Y.H. Chemical constituents from *Canarium pimela* fruits. *J. Chin. Med. Mater.* 2014, 37, 1801–1803.
43. Helene, T.; Serge, F.; Ngadjui, B.T.; Etienne, D.; Abegaz, B.M. Phenolic metabolites from the seeds of *Canarium schweinfurthii*. *Bull. Chem. Soc. Ethiop.* 2000, 14, 155–159. [CrossRef]
44. Shaari, K.; Waterman, P.G. Podophyllotoxin-type lignans as major constituents of the stems and leaves of *Casearia clareka*. *J. Nat. Prod.* 1992, 57, 720–724. [CrossRef]
45. Cao, S.G.; Sim, K.Y.; Goh, S.H. Biflavonoids of *Calophyllum venulosum*. *J. Nat. Prod.* 1997, 60, 1245–1250. [CrossRef]
46. Ma, Z.W.; He, G.F.; Yin, W.F. Studies on biflavonoids of the leaves of *Cephalotaxus fortunei* Hook. F. var. *alpina* native to China. *Acta Bot. Sinica* 1986, 24, 416–418.
47. Lee, M.K.; Lim, S.W.; Yang, H.; Sung, S.H.; Lee, H.S.; Park, M.J.; Kim, Y.C. Osteoblast differentiation stimulating activity of biflavonoids from *Cephalotaxus koreana*. *Bioorg. Med. Chem. Lett.* 2006, 16, 2850–2854. [CrossRef] [PubMed]
48. Ma, Z.W.; He, G.F.; Yin, W.F. Olivariflavone, a new biflavonoid from *Cephalotaxus oliveri* Mast. *Acta Bot. Sin.* 1986, 28, 641–645.
49. Krauze-Baranowska, M.; Boblocka, L.; El Hela, A.A. Biflavones from *Chamaecyparis obtusa*. *Z. Naturforsch.* C 2005, 60, 679–685. [CrossRef] [PubMed]
50. Ishola, I.O.; Agbaje, O.E.; Narender, T.; Adeyemi, O.O.; Shukla, R. Bioactivity guided isolation of analgesic and anti-inflammatory constituents of *Cnestis ferruginea* leaves. *Nat. Prod. Res.* 2014, 28, 142–147. [CrossRef] [PubMed]
51. Zhang, M.; Liu, J.; Liu, P.; Liu, J.P.; Xin, H.L.; Zhang, L.; Wang, Y.L.; Tang, K.X. Study on chemical constituents of the branches and leaves of *Cunninghamia lanceolata*. *J. Shanghai Jiaotong Univ.* 2011, 29, 67–71.
52. Krauze-Baranowska, M.; Cisowski, W.; Wiwart, M.; Madziar, B. Antifungal biflavones from *Cupressoscyaris leylandii*. *Planta Med.* 1999, 65, 572–573. [CrossRef] [PubMed]
53. Li, R.J.; Li, Y.; Wang, X.L. Study on the chemical constituents of *Cupressus chengiana* S.Y.Hu. *J. Southwest Univ. Natl.* 2014, 40, 523–526.
54. Ibrahim, N.A.; El-Seedi, H.R.; Mohammed, M.M. Phytochemical investigation and hepatoprotective activity of *Cupressus sempervirens* L. leaves growing in Egypt. *Nat. Prod. Res.* 2007, 21, 857–866. [CrossRef] [PubMed]
55. Das, B.; Mahender, G.; Rao, Y.K.; Tirupathi, P. Studies on phytochemicals, part 58. A new biflavonoid from *Cycas beddomei*. *Indian J. Chem.* B 2006, 45, 1933–1935.
56. Moawad, A.; Hetta, M.; Zjawiony, J.K.; Jacob, M.R.; Hifnawy, M.; Marais, J.P.; Ferreira, D. Phytochemical investigation of *Cycas circinalis* and *Cycas revoluta* leaflets: moderately active antibacterial biflavonoids. *Planta Med.* 2010, 76, 796–802. [CrossRef] [PubMed]
57. Zhou, Y.; Zhang, X.R.; Jiang, S.Y.; Li, C.L.; Peng, S.L. Chemical constituents of Cycas panzhihuaensis. Chin. J. Appl. Environ. Biol. 1999, 5, 367–370.

58. Laishram, S.; Sheikh, Y.; Moirangthem, D.S.; Deb, L.; Pal, B.C.; Talukdar, N.C.; Borah, J.C. Anti-diabetic molecules from Cycas pectinata Griff. traditionally used by the Maiba-Maibi. Phytomedicine 2015, 22, 23–26. [CrossRef] [PubMed]

59. Chaabi, M.; Antheaume, C.; Weniger, B.; Justiniano, H.; Lugnier, C.; Lobstein, A. Biflavones of Decussocarpus rospigliosii as phosphodiesterases inhibitors. Planta Med. 2007, 73, 1284–1286. [CrossRef] [PubMed]

60. Tian, Y.; Tang, H.F.; Qiu, F.; Wang, X.J.; Xue, G.J.; Li, J. Antibacterial constituents of the aerial parts of Discocelidion rufescens. J. Shenying Pharm. Univ. 2009, 26, 191–195.

61. Mbaveng, A.T.; Ngameni, B.; Kuete, V.; Simo, I.K.; Ambassa, P.; Roy, R.; Bezabih, M.; Etoa, F.X.; Ngadjui, B.T.; Abegaz, B.M.; et al. Antimicrobial activity of the crude extracts and five flavonoids from the twigs of Dorstenia barteri (Moraceae). J. Ethnopharmacol. 2008, 116, 483–489. [CrossRef] [PubMed]

62. Ng’ang’a, M.M.; Hussain, H.; Chhabra, S.; Langat-Thoruwa, C.; Irungu, B.N.; Al-Harrasi, A.; Riaz, M.; Krohn, K. Antiplasmodial activity of compounds from Drypetes gerrardii. Chem. Nat. Compd. 2012, 48, 339–340. [CrossRef]

63. Zhang, Q.L.; Bai, X.C.; Cao, X.L.; Yun, Y. Chemical constituents from the fruits of Dorstenia henianensis stems and leaves. J. Chin. Med. Mater. 2015, 38, 2095–2097.

64. Ling, S.K.; Fukumori, S.; Tomii, K.; Tanaka, T.; Kouno, I. Isolation, purification and identification of chemical constituents from Elateriospermum indicum. J. Trop. For. Sci. 2006, 18, 81–85.

65. Jiang, S.J.; Wei, F.; Lu, J.; Lin, R.C.; Zhang, Z.J. Chemical studies on the Galeobdolon chinense. J. China Pharm. Univ. 2002, 33, 487–488.

66. Al-Shagdari, A.; Alarcón, A.B.; Cuesta-Rubio, O.; Piccinelli, A.L.; Rastrelli, L. Biflavonoids, main constituents from Garcinia barkeriana leaves. Nat. Prod. Commun. 2013, 8, 1237–1240. [PubMed]

67. Abderamane, B.; Tih, A.E.; Ghogomu, R.T.; Blond, A.; Bodo, B. New flavonoid C–O–C dimers and other chemical constituents from Garcinia brevipedicellata stem heartwood. Z. Naturforsch. C 2016, 71, 233–241. [CrossRef] [PubMed]

68. Shen, J.; Yang, J.S. Chemical constituents from fruits of Garcinia cowa. Chin. Pharm. J. 2006, 41, 660–661.

69. Abe, F.; Nagafuji, S.; Okabe, H.; Akahane, H.; Estrada-Muniz, E.; Huerta-Reyes, M.; Reyes-Chilpa, R. Trypanocidal constituents in plants 3. Leaves of Garcinia intermedia and heartwood of Calophyllum brasiliense. Biol. Pharm. Bull. 2004, 27, 141–143. [CrossRef] [PubMed]

70. Kaikabo, A.A.; Elloff, J.N. Antibiocidal activity of two biflavonoids from Garcinia livingstonei leaves against Mycobacterium smegmatis. J. Ethnopharmacol. 2011, 138, 253–255. [CrossRef] [PubMed]

71. Yang, H.; Figueroa, M.; To, S.; Baggett, S.; Jiang, B.; Basile, M.J.; Weinstein, I.B.; Kennelly, E.J. Benzophenones and biflavonoids from Garcinia livingstonei fruits. J. Agric. Food Chem. 2010, 58, 4749–4755. [CrossRef] [PubMed]

72. Trisuwon, K.; Rukachaisirikul, V.; Phongpaichit, S.; Hutadilok-Towatana, N. Tetraoxygenated xanthones and biflavonoids from the twigs of Garcinia merguensis. Phytochem. Lett. 2013, 6, 511–513. [CrossRef]

73. Ito, T.; Yokota, R.; Watarai, T.; Mori, K.; Oyama, M.; Nagasawa, H.; Matsuda, H.; Inuma, M. Isolation of six isoprenylated biflavonoids from the fruits of Trypanosoma brucei. Mosquito Res. 2011, 41, 551–558. [PubMed]

74. Baggett, S.; Protiva, P.; Mazzola, E.P.; Yang, H.; Ressler, E.T.; Basile, M.J.; Weinstein, I.B.; Kennelly, E.J. Bioactive benzophenones from Garcinia xanthochymus fruits. J. Nat. Prod. 2005, 68, 354–360. [CrossRef] [PubMed]

75. Lobstein-Guth, A.; Briançon-Scheid, F.; Victoire, C.; Haag-Berrurier, M.; Anton, R. Isolation of amentoflavone from Ginkgo biloba. Planta Med. 1998, 54, 555–556. [CrossRef] [PubMed]

76. Fritz, D.; Venturi, C.R.; Cargin, S.; Schripsema, J.; Roehe, P.M.; Montanha, J.A.; von Poser, G.L. Hexaploid virus inhibitory substances from Hypericum connatum Lam., a plant used in southern Brazil to treat oral lesions. J. Ethnopharmacol. 2007, 113, 517–520. [CrossRef] [PubMed]

77. Berghöfer, R.; Hölzl, J. Isolation of 3′, 18′-Biapigenin (Amentoflavone) from Hypericum perforatum. Planta Med. 1989, 55, 91. [CrossRef]

78. Kuroshima, K.N.; Campos-Buzzi, F.; Yunes, R.A.; Delle Monache, F.; Cecinell, V. Chemical composition and antinociceptive properties of Hyeronima alchorneoides leaves. Pharm. Biol. 2005, 43, 573–578. [CrossRef]
97. Gu, Y.L.; Xu, Y.M.; Fang, S.D. The chemical constituents from

96. Liu, J.J.; Liu, X.K. Chemical constituents from edible part of

95. Pegnyemb, D.E.; Mbing, J.N.; Atchade, A.D.; Tih, R.G.; Sondengam, B.L.; Blond, A.; Bodo, B. Antimicrobial

94. Velandia, J.R.; de Carvalho, M.G.; Braz-Filho, R.; Werle, A.A. Biflavonoids and a glucopyranoside derivative

93. De Araujo, M.F.; dos Santos, C.B.; Cavalcanti, J.F.; Pereira, F.S.; Mendes, G.S.; Werle, A.A.; Romanos, M.T.V.;

92. Pinto, M.E.F.; da Silva, M.S.; Schindler, E.; Barbosa, J.M.; El-Bacha, R.D.; Castello-Branco, M.V.S.; Agra, M.D.;

91. Morita, N.; Shimizu, M.; Arisawa, M.; Shirataki, Y. Isolation of ametoflavone and 2 new glycosides from

90. Krauze-Baranowska, M.; Mardarowicz, M.; Wiwart, M. The chemical composition of Microbiota decussata.

89. Li, S.S.; Dai, H.F.; Zhao, Y.X.; Zuo, W.J.; Li, X.N.; Mei, W.L. Chemical constituents from the stems of Cassava

88. Ge, D.D.; Zhang, Y.; Yin, M.; Chen, Y.; Zhao, X.Z.; Dong, Y.F. A biflavonoid from stems and leaves of Lonicera macranthoides. Chem. Nat. Compd. 2012, 48, 231–233. [CrossRef]

87. Gao, F.F.; Zhao, D.; Deng, J. New flavonoids from<br>Phytochemistry 2005, 66, 1922–1926. [CrossRef] [PubMed]

86. De Oliveira, M.C.C.; de Carvalho, M.G.; da Silva, C.J.; Werle, A.A. New biflavonoid and other constituents from Lysimachia christinae. Z. Naturforsch. C 2002, 57, 998–1003. [CrossRef] [PubMed]

85. Zheng, G.Y.; Ma, Y.Y.; Mu, X.R.; Lu, X.L.; Zhai, M. Study on the chemical constituents of Nandina domestica. J. Chin. Med. Mater. 2002, 13, 119–123. [CrossRef]

84. Ge, D.D.; Zhang, Y.; Liu, E.W.; Wang, T.; Hu, L.M. Chemical constituents of Mangifera indica leaves (I). Chin. Tradit. Herb. Drugs 2011, 42, 428–431.

83. Jiang, Y.; Qian, Z.M.; Zhang, T.D.; Li, P. Chemical constituents in aerial parts of Lonicera chrysanthana Turcz (II). Chem. Ind. For. Prod. 2008, 28, 58–60.

82. Wang, P.P.; Luo, J.; Yang, M.H.; Kong, L.Y. Chemical constituents of<br>Chem. Pharm. Bull. 2008, 28, 794–797. [CrossRef]

81. Dora, G.; Edwards, J.M. Taxonomic status of Retrophyllum rospigliosii and Lonicera ternatus (Velloziaceae). J. Brazil. Chem. Soc. 2011, 22, 1819–1824. [CrossRef]

80. Jeong, E.J.; Seo, H.; Yang, H.; Kim, J.; Sung, S.H.; Kim, Y.C. Anti-inflammatory phenolics isolated from Juniperus rigida leaves and twigs in lipopolysaccharide-stimulated RAW264.7 macrophage cells. J. Enzym. Inhib. Med. Chem. 2012, 27, 875–879. [CrossRef] [PubMed]

79. Nakanishi, T.; Inatomi, Y.; Murata, H.; Iida, N.; Inada, A.; Lang, F.A.; Murata, J. Phytochemical study on American plants I. Two new phenol glucosides, together with known biflavones and diterpene, from leaves of Juniperus communis Hook. Chem. Pharm. Bull. 2002, 50, 1358–1361. [CrossRef] [PubMed]

78. Wang, P.; Luo, J.; Yang, M.H.; Kong, L.Y. Chemical constituents of<br>Chem. Ind. For. Prod. 2008, 28, 58–60. [CrossRef]

77. Song, Y.L.; Jiang, Y.; Bi, D.; Tian, X.; Liang, L.J.; Tu, P.F. Chemical constituents from n-butanol extract of aerial part of Polyspora sibirica. China J. Chin. Mater. Med. 2012, 37, 471–474.

76. Xiong, Y.; Deng, K.Z.; Guo, Y.Q.; Gao, W.Y. Studies on chemical constituents of flavonoids and glycosides in Ranunculus ternatus. Chin. Tradit. Herb. Drugs 2008, 39, 1449–1452.

75. Amaro-Luis, J.M.; Amesty, A.; Balsas, A.; Montealegre, R. Biflavones from the leaves of Retrophyllum rospigliosii. Biochem. Syst. Ecol. 2008, 36, 235–237. [CrossRef]

74. Svenningsen, A.B.; Madsen, K.D.; Liljefors, T.; Stafford, G.I.; van Staden, J.; Jager, A.K. Biflavones from Rhus species with affinity for the GABA(A)/benzodiazepine receptor. J. Ethnopharmacol. 2006, 103, 276–280. [CrossRef] [PubMed]

73. Lin, Y.M.; Anderson, H.; Flavin, M.T.; Pai, Y.H.; Mata-Greenwood, E.; Pengsuparp, T.; Pezzuto, J.M.; Schinazi, R.F.; Hughes, S.H.; Chen, F.C. In vitro anti-HIV activity of biflavonoids isolated from Rhus succedanea and Garcinia multiflora. J. Nat. Prod. 1997, 60, 884–888. [CrossRef] [PubMed]
103. Fu, J.S.; Lin, Y.; Han, H.D.; Hu, H.Q.; Wang, X.L. Chemical constituents in twigs and leaves of *Sabina pingii* var. *wilsonii*. *Chin. Tradit. Herb. Drugs* 2012, 43, 1724–1726.
104. Ma, Y.Y.; Fu, J.S.; Shan, X.Q.; Wang, L.; Wang, B.; Wang, X.L. Study on chemical constituents of *Sabina sinoalpina*. *Chin. Tradit. Herb. Drugs* 2010, 41, 32–36.
105. Zhao, J.; Yan, M.; Huang, Y.; He, W.Y.; Zhao, Y. Flavonoids from the leaves of *Sabina vulgaris* Antoine. *Chem. Ind. For. Prod.* 2008, 28, 33–37.
106. Swamy, R.C.; Kunert, O.; Schuhly, W.; Bucar, F.; Ferreira, D.; Rani, V.S.; Kumar, B.R.; Rao, A.V.N.A. Structurally unique biflavonoids from *Selaginella chrysocaulos* and *Selaginella bryopteris*. *Chem. Biodivers.* 2006, 3, 405–413. [CrossRef] [PubMed]
107. Lin, L.C.; Kuo, Y.C.; Chou, C.J. Cytotoxic biflavonoids from *Selaginella delicatula*. *J. Nat. Prod.* 2000, 63, 627–630. [CrossRef] [PubMed]
108. López-Sáez, J.A.; Pérez-Alonso, M.J.; Negueruela, A.V. Biflavonoids of *Selaginella denticulata* growing in Spain. *Z. Naturforsch.* C 1994, 49, 267–270.
109. Lin, R.C.; Skaltsounis, A.L.; Seguin, E.; Tillequin, F.; Koch, M. Phenolic Constituents of *Selaginella doederleini*. *Planta Med.* 1994, 60, 168–170. [CrossRef] [PubMed]
110. Lu, M.X.; Huang, K.L.; Shi, S.Y.; Zhang, H. Study on the chemical constituents of *Selaginella involvens* Spring and antibacterial activity. *Nat. Prod. Res. Dev.* 2009, 21, 973–975.
111. Tan, W.J.; Xu, J.C.; Li, L.; Chen, K.L. Bioactive compounds of inhibiting xanthine oxidase from *Selaginella labrlei*. *Nat. Prod. Res.* 2009, 23, 393–398. [CrossRef] [PubMed]
112. Sun, C.M.; Syu, M.J.; Huang, Y.T.; Chen, C.C.; Ou, J.C. Selective cytotoxicity of ginkgetin from *Selaginella moellendorffii*. *J. Nat. Prod.* 1997, 60, 382–384. [CrossRef] [PubMed]
113. Aguilar, M.I.; Benítez, W.V.; Colín, A.; Bye, R.; Rios-Gómez, R.; Calzada, F. Evaluation of the diuretic activity and antibacterial activity of *Selaginella nothohybrida* and *Selaginella lepidophylla* and its effects with ciclooxigenases inhibitors. *J. Ethnopharmacol.* 2015, 163, 167–172. [CrossRef] [PubMed]
114. Gao, X.J.; Hu, X.L.; Wang, K.W. Biflavonoid constituents from *Selaginella remotifolia* Spring. *Chin. Pharm. J.* 2016, 51, 1739–1743.
115. López-Sáez, J.A.; Pérez-Alonso, M.J.; Negueruela, A.V. The biflavonoid pattern of *Selaginella selaginoides*. *Z. Naturforsch.* C 1994, 49, 265–266.
116. Ma, S.C.; But, P.P.H.; Ooi, V.E.C.; He, Y.H.; Lee, S.H.S.; Lee, S.F.; Lin, R.C. Antiviral ameflavon from *Selaginella sinensis*. *Biol. Pharm. Bull.* 2001, 24, 311–312. [CrossRef] [PubMed]
117. Liu, H.Q.; Lin, R.C.; Ma, S.C.; Feng, F. Studies on chemical constituents of *Selaginella stauntoniana* (I). *Chin. Tradit. Herb. Drugs* 2003, 34, 298–299.
118. Kang, D.G.; Yin, M.H.; Oh, H.; Lee, D.H.; Lee, H.S. Vasorelaxation by ameflavone isolated from *Selaginella tamariscina*. *Planta Med.* 2004, 70, 718–722. [CrossRef] [PubMed]
119. Zheng, J.X.; Zheng, Y.; Zhi, H.; Dai, Y.; Wang, N.L.; Fang, Y.X.; Du, Z.Y.; Zhang, K.; Li, M.M.; Wu, L.Y.; et al. New 3′,8′-linked biflavonoids from *Selaginella uncinata* displaying protective effect against Anoxia. *Molecules* 2011, 16, 6204–6214. [CrossRef] [PubMed]
120. Silva, G.L.; Chai, H.; Gupta, M.P.; Farnsworth, N.R.; Cordell, G.A.; Pezzuto, J.M.; Beecher, C.W.; Kinghorn, A.D. Cytotoxic biflavonoids from *Selaginella willdenowii*. *Phytochemistry* 1995, 40, 129–134. [CrossRef]
121. Liu, Y.M.; Zhao, Y.Y.; Fan, Y.B.; Wang, X.; Cai, L.N. Flavonoids from *Speranskia Tuberculata*. *J. Chin. Pharm. Sci.* 1997, 6, 70–74.
122. Ayers, S.; Zink, D.L.; Mohn, K.; Powell, J.S.; Brown, C.M.; Murphy, T.; Brand, R.; Pretorius, S.; Stevenson, D.; Thompson, D.; et al. Flavonones from *Struthiola argentea* with anthelmintic activity in vitro. *Phytochemistry* 2008, 69, 541–545. [CrossRef] [PubMed]
127. Krauze-Baranowska, M.; Wiwart, M. Antifungal activity of biflavones from Taxus baccata and Ginkgo biloba. Z. Naturforsch. C 2003, 58, 65–69. [CrossRef] [PubMed]
128. Jung, S.H.; Kim, B.J.; Lee, E.H.; Osborne, N.N. Isoquercitrin is the most effective antioxidant in the plant Thuja orientalis and able to counteract oxidative-induced damage to a transformed cell line (RGC-5 cells). Neurosci. Int. 2010, 57, 713–721. [CrossRef] [PubMed]
129. Xu, G.H.; Ryoo, I.J.; Kim, Y.H.; Choo, S.J.; Yoo, I.D. Free radical scavenging and antielastase activities of flavonoids from the fruits of Thuja orientalis. Arch. Pharm. Res. 2009, 32, 275–282. [CrossRef] [PubMed]
130. Voirin, B.; Jay, M. Presence of amentoflavone in Tmesipterus tannensis. Phytochemistry 1977, 16, 2043–2044. [CrossRef]
131. Ryu, Y.B.; Jeong, H.J.; Kim, J.H.; Kim, Y.M.; Park, J.Y.; Kim, D.; Nguyen, T.T.; Park, S.J.; Chang, J.S.; Park, K.H.; et al. Biflavonoids from Torreya nucifera displaying SARS-CoV 3CL(pro) inhibition. Bioorg. Med. Chem. 2010, 18, 7940–7947. [CrossRef] [PubMed]
132. Li, S.H.; Zhang, H.J.; Niu, X.M.; Yao, P.; Sun, H.D.; Fong, H.H.S. Chemical constituents from Amentotaxus yunnanensis and Torreya yunnanensis. J. Nat. Prod. 2003, 66, 1002–1005. [CrossRef] [PubMed]
133. Tomassini, L.; Gao, J.; Foddaï, S.; Serafini, M.; Ventrone, A.; Nicoletti, M. Iridoid glucosides from Viburnum chinshanense. Nat. Prod. Res. 2006, 20, 697–700. [CrossRef] [PubMed]
134. Jang, H.; Lee, J.W.; Jin, Q.H.; Kim, S.Y.; Lee, D.; Hong, J.T.; Kim, Y.; Lee, M.K.; Hwang, B.Y. Biflavones and furanone glucosides from Zabelia tayagi. Helv. Chim. Acta 2015, 98, 1419–1425. [CrossRef]
135. Ruan, X.; Yan, L.Y.; Li, X.X.; Liu, B.; Zhang, H.; Wang, Q. Optimization of process parameters of extraction of amentoflavone, queretin and ginkgetin from Taxus chinensis using supercritical CO2 plus co-solvent. Molecules 2014, 19, 17682–17696. [CrossRef] [PubMed]
136. Bi, W.; Tian, M.; Row, K.H. Evaluation of alcohol-based deep eutectic solvent in extraction and determination of flavonoids with response surface methodology optimization. J. Chromatogr. A 2013, 1285, 22–30. [CrossRef] [PubMed]
137. Yi, M.L.; Sheng, X.F.; Xu, K.P.; Tan, G.S.; Zou, H. Flavonoids from Selaginella uncinata. China J. Chin. Mater. Med. 2015, 40, 3005–3008.
138. Li, S.G.; Zhao, M.F.; Li, Y.X.; Sui, Y.X.; Yao, H.; Huang, L.Y.; Lin, X.H. Preparative isolation of six anti-tumour biflavonoids from Selaginella doederleinii Hieron by high-speed counter-current chromatography. Phytochem. Anal. 2014, 25, 127–133. [CrossRef] [PubMed]
139. Wang, J.; Liu, S.; Ma, B.; Chen, L.N. Rapid screening and detection of XOD inhibitors from S. tamariscina by ultrafiltration LC-PDA-ESI-MS combined with HPCCC. Anal. Bioanal. Chem. 2014, 406, 7379–7387. [CrossRef] [PubMed]
140. Hyun, S.K.; Jung, H.A.; Chung, H.Y.; Choi, J.S. In vitro peroxyxynitrite scavenging activity of 6-hydroxykynurenic acid and other flavonoids from Ginkgo biloba yellow leaves. Arch. Pharm. Res. 2006, 29, 1074–1079. [CrossRef] [PubMed]
141. Kunert, O.; Swamy, R.C.; Kaiser, M.; Presser, A.; Buzzi, S.; Rao, A.V.N.A.; Schuhly, W. Antiplasmodial and leishmanicidal activity of biflavonoids from Indian Selaginella bryopteris. Phytochem. Lett. 2008, 1, 171–174. [CrossRef]
142. Song, R.; Liu, L.F.; Ma, H.Y.; Fan, S.Y.; Wang, H. Chemical Constituents of Selaginella mollendorfii. Pharm. Clin. Res. 2016, 24, 318–320.
143. Zou, Z.X.; Xu, K.P.; Zou, H.; Zhang, Q.; Liu, M.Z.; Tan, G.S. Biflavonoids from Selaginella moellendorfii Hieron. Cent. South Pharm. 2012, 10, 4–6.
144. Camacho, M.D.; Mata, R.; Castaneda, P.; Kirby, G.C.; Warhurst, D.C.; Croft, S.L.; Phillipson, J.D. Bioactive compounds from Celaenodontron mexicanum. Planta Med. 2000, 66, 463–468. [CrossRef] [PubMed]
145. Gu, S.H.; Zhang, D.; Xu, L.Z.; Yang, S.L. Study on chemical constituents of Podocarpus brevifolius. Chin. Tradit. Herb. Drugs 1997, 28, 586–588.
146. Pattamadilok, D.; Suttisri, R. Seco-terpenoids and other constituents from Elaterispermum tapos. J. Nat. Prod. 2008, 71, 292–294. [CrossRef] [PubMed]
147. Xu, Y.M.; Fang, S.D.; He, Q.M. The chemical constituents in Dacrydium pierrei. Acta Bot. Sin. 1991, 33, 646–648.
148. Cheng, X.L.; Ma, S.C.; Yu, J.D.; Yang, S.Y.; Xiao, X.Y.; Hu, J.Y.; Lu, Y.; Shaw, P.C.; But, P.P.; Lin, R.C. Selaginellin A and B, two novel natural pigments isolated from Selaginella tamariscina. Chem. Pharm. Bull. 2008, 56, 982–984. [CrossRef] [PubMed]
149. Zhao, Q.; Wang, C.X.; Li, Y.L.; Liu, C.Y.; Rong, Y.H. Chemical constituents from Selaginella doederleinii and their bioactivities. Chin. Tradit. Herb. Drugs 2013, 44, 3270–3275.

150. Liu, X.Q.; Zhang, X.D.; Zhu, Y.L.; Shin, B.Y.; Wu, S.X. Structure identification of biflavones and determination of taxol from Taxus nadii. J. Chin. Med. Mat. 2008, 31, 1499–1501.

151. Bagla, V.P.; McGaw, L.J.; Elgorashi, E.E.; Ellof, J.N. Antimicrobial activity, toxicity and selectivity index of two biflavonoids and a flavone isolated from Podocarpus henkelii (Podocarpaceae) leaves. BMC Complement. Altern. Med. 2014, 14. [CrossRef] [PubMed]

152. Xu, Y.M.; Fang, S.D. The chemical constituents from Podocarpus nagi (II). Acta Bot. Sin. 1991, 33, 406–408.

153. Parmar, V.S.; Vardhan, A.; Bisht, K.S.; Sharma, N.K.; Jain, R.; Taneja, P.; Tyagi, O.D.; Boll, P.M. A rare biflavone from Taxus baccata. Indian J. Chem. B 1993, 32, 601–603.

154. Glensk, M.; Wlodarczyk, M.; Stefanowicz, P.; Kucharska, A. Biflavonoids from the Wollemi Pine, Wollemia nobilis (Araucariaceae). Biochem. Syst. Ecol. 2013, 46, 18–21. [CrossRef]

155. Lee, C.W.; Choi, H.J.; Kim, H.S.; Kim, D.H.; Chang, I.S.; Moon, H.T.; Lee, S.Y.; Oh, W.K.; Woo, E.R. Biflavonoids isolated from Selaginella tamariscina regulate the expression of matrix metalloproteinase in human skin fibroblasts. Bioorg. Med. Chem. 2008, 16, 732–738. [CrossRef] [PubMed]

156. Yang, J.W.; Pokharel, Y.R.; Kim, M.R.; Woo, E.R.; Choi, H.K.; Kang, K.W. Inhibition of inducible nitric oxide synthase by sumaflavone isolated from Selaginella tamariscina. J. Ethnopharmacol. 2006, 105, 107–113. [CrossRef] [PubMed]

157. Markham, K.R. The structures of amentoflavone glycosides isolated from Psilotum nudum. Phytochemistry 1984, 23, 2053–2056. [CrossRef]

158. Kuo, Y.H.; Lin, C.H.; Hwang, S.Y.; Shen, Y.C.; Lee, Y.L.; Li, S.Y. A novel cytotoxic C-methylated biflavone from the stem of Cephalotaxus wilsoniana. Chem. Pharm. Bull. 2000, 48, 440–441. [CrossRef] [PubMed]

159. Moawad, A.; Hetta, M.; Zjawiony, J.K.; Ferreira, D.; Hifnawy, M. Two new dihydroamentoflavone glycosides from Cyas revoluta. Nat. Prod. Res. 2014, 28, 41–47. [CrossRef] [PubMed]

160. Fan, X.L.; Xu, J.C.; Lin, X.H.; Chen, K.L. Study on Biflavonoids from Selaginella uncinata (Desv.) Spring. Chin. Pharm. J. 2009, 44, 15–19. [CrossRef] [PubMed]

161. Das, B.; Mahender, G.; Rao, Y.K.; Prabhakar, A.; Jagadeesh, B. Biflavonoids from Cycas beddomei. Chem. Pharm. Bull. 2005, 53, 135–136. [CrossRef] [PubMed]

162. Tang, T.; Na, Z.; Xu, Y.K. Chemical constituents from Dysoxylum cauliflorum (Meliaceae). Nat. Prod. Res. Dev. 2012, 24, 777–779.

163. Kim, J.H.; Tai, B.H.; Yang, S.Y.; Kim, J.E.; Kim, S.K.; Kim, Y.H. Soluble Epoxide Hydrolase Inhibitory Constituents from Selaginella tamariscina. B. Korean Chem. Soc. 2015, 36, 300–304. [CrossRef]

164. Ishola, I.O.; Chaturvedi, J.P.; Rai, S.; Rajasekar, N.; Adeyemi, O.O.; Shukla, R.; Narendar, T. Evaluation of amentoflavone isolated from Cnestis ferruginea. In Vivo 2013, 27, 761506. [CrossRef] [PubMed]

165. Li, X.C.; Wang, L.; Han, W.J.; Mai, W.Q.; Han, L.; Chen, D.F. Amentoflavone protects against hydroxyl radical-induced DNA damage via antioxidant mechanism. Turk. J. Biochem. 2014, 39, 30–36. [CrossRef]

166. Oh, J.; Rho, H.S.; Yang, Y.; Yoon, J.Y.; Lee, J.; Hong, Y.D.; Kim, H.C.; Choi, S.S.; Kim, T.W.; Shin, S.S.; et al. Extracellular signal-regulated kinase is a direct target of the anti-inflammatory compound amentoflavone derived from Torreya nucifera. Mediat. Inflamm. 2013, 2013, 761506. [CrossRef] [PubMed]

167. Li, X.C.; Wang, L.; Han, W.J.; Mai, W.Q.; Han, L.; Chen, D.F. Amentoflavone protects against hydroxyl radical-induced DNA damage via antioxidant mechanism. Turk. J. Biochem. 2014, 39, 30–36. [CrossRef]

168. Pei, J.S.; Liu, C.C.; Hsu, Y.N.; Lin, L.L.; Wang, S.C.; Chung, J.G.; Bau, D.T.; Lin, S.S. Amentoflavone induces cell-cycle arrest and apoptosis in MCF-7 human breast cancer cells via mitochondria-dependent pathway. In Vivo 2012, 26, 963–970. [PubMed]

169. Siveen, K.S.; Kuttan, G. Effect of Amentoflavone, a phenolic component from Biophyrum sensitivum, on cell cycling and apoptosis of B16F-10 melanoma cells. J. Environ. Pathol. Toxicol. Oncol. 2011, 30, 301–309. [CrossRef] [PubMed]

170. Lee, J.S.; Lee, J.S.; Oh, W.K.; Sul, J.Y. Fatty acid synthase inhibition by amentoflavone induces apoptosis and antiproliferation in human breast cancer cells. Biol. Pharm. Bull. 2009, 32, 1427–1432. [CrossRef] [PubMed]
171. Lee, C.W.; Na, Y.; Park, N.H.; Kim, H.S.; Ahn, S.M.; Kim, J.W.; Kim, H.K.; Jang, Y.P. Amentoflavone inhibits UVB-induced matrix metalloproteinase-1 expression through the modulation of AP-1 components in normal human fibroblasts. *Appl. Biochem. Biotechnol.* 2012, 166, 1137–1147. [CrossRef] [PubMed]

172. Zheng, X.K.; Su, C.F.; Zhang, L.; Gao, A.S.; Ke, Y.Y.; Yuan, P.P.; Wang, X.L.; Zhang, X.; Feng, W.S. Anti-diabetic activity of amentoflavone in *Selaginella tamariscina* in diabetic mice. *Chin. J. Exp. Tradit. Med. Formaeae* 2013, 19, 198–202.

173. Na, M.; Kim, K.A.; Oh, H.; Kim, B.Y.; Oh, W.K.; Ahn, J.S. Protein tyrosine phosphatase 1B inhibitory activity of amentoflavone and its cellular effect on tyrosine phosphorylation of insulin receptors. *Biol. Pharm. Bull.* 2007, 30, 379–381. [CrossRef] [PubMed]

174. Wilsky, S.; Sobotta, K.; Wiesener, N.; Pilas, J.; Althof, N.; Munder, T.; Wutzler, P.; Henke, A. Inhibition of fatty acid synthase by amentoflavone reduces coxsackievirus B3 replication. *Arch. Virol.* 2012, 157, 259–269. [CrossRef] [PubMed]

175. Ishola, I.O.; Chatterjee, M.; Tota, S.; Tadigopulla, N.; Adeyemi, O.O.; Palit, G.; Shukla, R. Protective effect of *Selaginella tamariscina* on scopolamine-induced memory impairment in mice: A behavioral and biochemical study. *Pharm. Biol.* 2013, 51, 825–835. [CrossRef] [PubMed]

176. Ishola, I.O.; Tota, S.; Adeyemi, O.O.; Agbaje, E.O.; Narender, T.; Shukla, R. Protective effect of *Cnestis ferruginea* and its active constituent on scopolamine-induced memory impairment in mice: A behavioral and biochemical study. *Pharm. Biol.* 2013, 51, 825–835. [CrossRef] [PubMed]

177. Jeong, E.J.; Hwang, L.; Lee, M.; Lee, K.Y.; Ahn, M.J.; Sung, S.H. Neuroprotective biflavonoids of *Chamaecyparis obtusa* leaves against glutamate-induced oxidative stress in HT22 hippocampal cells. *Food Chem. Toxicol.* 2014, 64, 397–402. [CrossRef] [PubMed]

178. Xu, L.; Yin, M.H. Experiment study on vasodilative effects of amentoflavone ethyl acetate extract of *Selaginella tamariscina*. *J. Med. Sci. Yanbian Univ.* 2009, 32, 246–248.

179. Zheng, X.K.; Ning, T.L.; Wang, X.L.; Liu, C.X.; Liu, Y.Y.; Feng, W.S. Effects of total flavonoids and amentoflavone on the cytokine profile, NF-κB-mediated inflammation and keratinocyte proliferation. *Molecules* 2014, 19, 299 22 of 23

180. Saponara, R.; Bosisio, E. Inhibition of cAMP-phosphodiesterase by biflavones of *Ginkgo biloba* in rat adipose tissue. *J. Nat. Prod.* 1998, 61, 1386–1387. [CrossRef] [PubMed]

181. Kubota, Y.; Umegaki, K.; Tanaka, N.; Mizuno, H.; Nakamura, K.; Kunitomo, M.; Shinozuka, K. Safety of dietary supplements: Chronotropic and inotropic effects on isolated rat atria. *Biol. Pharm. Bull.* 2002, 25, 197–200. [CrossRef] [PubMed]

182. Yue, S.M.; Kang, W.Y. Lowering blood lipid and hepatoprotective activity of amentoflavone from *Selaginella tamariscina* in vivo. *J. Med. Plants Res.* 2011, 5, 3007–3014.

183. Zhang, J.; Liu, Z.; Cao, W.; Chen, L.; Xiong, X.; Qin, S.; Zhang, Z.; Li, X.; Hu, C.A. Amentoflavone inhibits angiogenesis of endothelial cells and stimulates apoptosis in hypertrophic scar fibroblasts. *Burns* 2014, 40, 922–929. [CrossRef] [PubMed]

184. An, J.; Li, Z.; Dong, Y.; Ren, J.; Huo, J. Amentoflavone protects against psoriasis-like skin lesion through suppression of NF-κB-mediated inflammation and keratinocyte proliferation. *Mol. Cell Biochem.* 2016, 413, 87–95. [CrossRef] [PubMed]

185. Sakhivel, K.M.; Guruvayoorappan, C. Amentoflavone inhibits iNOS, COX-2 expression and modulates cytokine profile, NF-κB signal transduction pathways in rats with ulcerative colitis. *Int. Immunopharmacol.* 2013, 17, 907–916. [CrossRef] [PubMed]

186. Zha, X.; Xu, Z.; Liu, Y.; Xu, L.; Huang, H.; Zhang, J.; Cui, L.; Zhou, C.; Xu, D. Amentoflavone enhances osteogenesis of human mesenchymal stem cells through JNK and p38 MAPK pathways. *J. Nat. Med.* 2016, 70, 634–644. [CrossRef] [PubMed]

187. Xu, P.; Jiang, E.J.; Wen, S.Y.; Lu, D.D. Amentoflavone acts as a radioprotector for irradiated v79 cells by regulating reactive oxygen species(ROS), cell cycle and mitochondrial mass. *Asian Pac. J. Cancer Prev.* 2014, 15, 7521–7526. [CrossRef] [PubMed]
190. Liao, S.; Ren, Q.; Yang, C.; Zhang, T.; Li, J.; Wang, X.; Qu, X.; Zhang, X.; Zhou, Z.; Zhang, Z.; et al. Liquid chromatography-tandem mass spectrometry determination and pharmacokinetic analysis of amentoflavone and its conjugated metabolites in rats. *J. Agric. Food Chem.* **2015**, *63*, 1957–1966. [CrossRef] [PubMed]

191. Wang, X.; Zhao, X.; Gu, L.; Lv, C.; He, B.; Liu, Z.; Hou, P.; Bi, K.; Chen, X. Simultaneous determination of five free and total flavonoids in rat plasma by ultra HPLC–MS/MS and its application to a comparative pharmacokinetic study in normal and hyperlipidemic rats. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2014**, *953–954*, 1–10. [CrossRef] [PubMed]

192. Zhou, X.; Chen, P.D.; Zhang, L.; Ding, A.W. HPLC fingerprint of Shixiao San. *Chin. J. Exp. Tradit. Med. Formuae* **2013**, *19*, 73–76.

193. Dai, Z.; Wang, G.L.; Ma, S.C.; Lu, J.; Lin, R.C. Determination of biflavonoids in Selaginellae plants by micellar electrokinetic capillary electrophoresis. *Chin. J. Pharm. Anal.* **2006**, *26*, 1408–1412.

194. Liu, H.Q.; Lin, R.C.; Feng, F.; Dang, H.Q. Determination of biflavones from Selaginella by HPLC. *Chin. J. Pharm. Anal.* **2002**, *22*, 392–395.

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