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The chemistry of flavonoids from Annonaceae: a comprehensive review

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The Annonaceae family, a major group of tropical and subtropical flowering plants, is widely recognized for its edible fruits and traditional medicinal uses. While phytochemical research on this family has primarily focused on alkaloids and acetogenins, flavonoids, key polyphenolic compounds with diverse pharmacological properties, have remained comparatively overlooked. This review presents the first comprehensive synthesis of flavonoid chemistry within Annonaceae, analyzing 238 reported structures across multiple genera and regions. Our findings reveal a surprisingly broad structural diversity, with flavonol glycosides and flavanones emerging as the most prevalent classes. Other types, including chalcones, isoflavanones, catechins, and dihydroflavonols, further underscore the family's underexplored chemical richness. Geographically, Asia dominates the research landscape, particularly Thailand and Vietnam, while Africa and the Americas also contribute notably. Among the most studied genera are *Uvaria*, *Melodorum*, *Fissistigma*, *Annona*, and *Desmos*. Leaf extracts represent the primary source of flavonoid isolation, though other plant parts remain underutilized. This review not only consolidates existing data but also highlights critical gaps in taxonomic coverage, biosynthetic understanding, and ecological context. By illuminating the hidden diversity and potential of flavonoids in Annonaceae, this work lays the groundwork for future studies in natural products chemistry, pharmacology, and plant systematics.

KEYWORDS

flavonols, flavanones, glycosides, *Uvaria*, *Annona*

1 Introduction

The Annonaceae family, commonly referred to as the custard apple family, is one of the largest and most morphologically diverse families of flowering plants within the order Magnoliales. Comprising over 2,500 species across approximately 108 genera (Nge et al., 2024), Annonaceae is widely distributed in tropical and subtropical regions and holds significant ecological, economic, and ethnobotanical value. Many species are known for producing edible fruits and have been used in traditional medicine systems throughout Africa, Asia, and the Americas (Hernández Fuentes et al., 2021; Al Kazman et al., 2022; Erkens et al., 2023).

Phytochemically, Annonaceae has been extensively studied for its isoquinoline-derived alkaloids, particularly aporphinoids and acetogenins, which are associated with a range of

biological activities, including cytotoxic, antimicrobial, antiparasitic, and anti-inflammatory effects (Leboeuf et al., 1980). However, while these chemical classes have garnered considerable scientific interest, other equally important groups of natural products remain comparatively understudied, such as flavonoids (Santos and Salatino, 2000). Flavonoids are polyphenolic compounds with well-established roles in plant physiology and human health (Harborne and Mabry, 2013; Panche et al., 2016). They are known for their antioxidant properties and associated pharmacological activities such as anti-inflammatory, antimicrobial, antidiabetic, and anticancer effects. In many plant families, flavonoids serve as key bioactive principles (Panche et al., 2016; Dias et al., 2021). Surprisingly, despite the biological and ecological relevance of flavonoids, their diversity and distribution within Annonaceae remain poorly understood.

The existing literature suggests that flavonoids, although confirmed in several Annonaceae genera (Santos and Salatino, 2000), have not been systematically investigated across the family. Most reports have focused on isolated findings from individual species, and no comprehensive survey has been conducted to elucidate the structural diversity, biosynthetic patterns, or taxonomic significance of flavonoids within Annonaceae. These findings underscore both the presence and potential significance of flavonoids in Annonaceae while simultaneously highlighting the need for broader and more integrative investigations.

Given the growing interest in plant-derived bioactive compounds and the rich ethnopharmacological background of Annonaceae (Silva et al., 2018a; Silva et al., 2018b; Leite et al., 2020; Mohanty et al., 2023; Mouafon et al., 2025), a systematic review of flavonoids in this family is timely. Such an effort can reveal untapped chemical diversity, inform future pharmacological studies, and contribute to our understanding of the ecological and evolutionary roles of flavonoids in this basal angiosperm lineage. This review aims to fill this knowledge gap by synthesizing the current state of research on flavonoids in Annonaceae. We begin by providing an overview of the family's classification and global distribution, followed by a discussion of its diagnostic features, economic significance, and general phytochemical profile. We then focus specifically on the occurrence, chemical structure, and biological activities of flavonoids identified in Annonaceae species to date, highlighting gaps in knowledge and proposing future research directions.

1.1 Classification and distribution of Annonaceae family

Annonaceae Juss. is a morphologically diverse family of flowering plants comprising 108 genera and approximately 2,500 species distributed in four subfamilies: Anaxagoreoideae (ca. 30 spp.), Ambavioideae (ca. 60 spp.), Malmeoideae (ca. 800 spp.), and Annonoideae (ca. 1,600 spp.). It is currently the most diverse family in the Magnoliales clade at both the genus and species levels and the most primitive family of angiosperms (Erkens et al., 2023; Nge et al., 2024). Since the formalization of plant family names with the publication of Genera plantarum by de Jussieu in 1789, Annonaceae has been recognized as a distinct and readily identifiable group (Chatrou et al., 2012a). In the past four decades, considerable progress has been made in understanding the systematics and taxonomy of the family, driven by an extensive and collaborative global research effort. As a result, Annonaceae has become one of the most taxonomically well-known tropical plant families (Nge et al., 2024). Undeniably, the understanding of evolutionary relationships within Annonaceae has benefited from advances in molecular phylogenetics (Chatrou et al., 2012b; Guo et al., 2017; Couvreur et al., 2019; Chaowasku, 2020; Dagallier et al., 2023).

A recent phylogenomic study employing a previously developed nuclear bait kit tailored for Annonaceae succeeded in constructing the first comprehensive genus-level phylogeny of the group (Nge et al., 2024). This study incorporated all 108 recognized genera and was based on hundreds of nuclear loci. The resulting tree led to important taxonomic revisions, including the recognition of 25 subtribes, 21 of which are newly proposed. The ability of this phylogenomic framework to clarify intertribal relationships within the subfamily Malmeoideae (Chaowasku, 2020) and to resolve most phylogenetic placements within the tribe Miliuseae (Guo et al., 2017) was a key achievement. Notably, the analysis indicated that *Meiocarpidium* is sister to Ambavioideae, warranting its elevation to tribal status rather than classification as a distinct subfamily. Moreover, the genus *Artabotrys*, previously aligned with the tribe Xylopieae based on plastid data, was instead placed within Duguetieae, where it forms a clade with the African genera *Letestudoxa* and *Pseudartabotrys* (Nge et al., 2024). In addition to these findings, the study also drew attention to considerable gene tree conflict, particularly near the base of certain clades. This conflict is likely associated with rapid early diversification within the tribe, resulting in extensive incomplete lineage sorting. Such complexities pose challenges for fully resolving the deeper phylogenetic relationships in the family (Nge et al., 2024).

Annonaceae species are widely distributed across tropical and subtropical regions, exhibiting particularly high species richness in tropical lowland rainforests, with their richness and abundance being associated with higher temperatures and increased precipitation (Al Kazman et al., 2022; Erkens et al., 2023; Nge et al., 2024). A recent study based on spatial data combined with published and drafted International Union for Conservation of Nature (IUCN) Red List assessments allowed for an investigation into how Annonaceae are distributed across a human-impacted globe and provided insight into how this taxon is distributed across natural biomes and anthropogenic biomes (anthromes) (Erkens et al., 2023). Based on records of 67,966 specimens, this study revealed that Annonaceae occur in nearly every tropical region and are present in four of the six major terrestrial biome types: the desert biome type, the grassland biome type, the temperate vegetation with trees biome type, and the tropical vegetation with trees biome type (Erkens et al., 2023). At the continental level, Central and South America, in particular, account for more than half (61%) of the specimens and, together with Africa (27%), represent over 85% of the total. Regarding genus distribution, it is noteworthy that only the genus *Xylopia* is present on all continents. In contrast, 78 out of the 108 genera have their specimens restricted to a single continent. A particularly interesting case is the genus *Asimina*, which is entirely distributed outside the tropical realm being found exclusively in North America (Erkens et al., 2023).

At the country level, Brazil holds the largest number of Annonaceae specimens, followed by Peru, Gabon, and the United States (Erkens et al., 2023). In Brazil, 33 genera and approximately 400 species are recorded, the vast majority of which occur in the northern region (292 species), especially in the state of Amazonas (214 species). The northeastern (119 species), central-western (87 species), and southeastern (95 species) regions also show significant occurrences, while the southern region has a lower incidence (24 species). Regarding phytogeographic domains, the Amazon rainforest harbors the highest number of species, followed by the Atlantic rainforest and the Central Brazilian savanna. The Caatinga, Pantanal, and Pampa domains host comparatively fewer species (Maas et al., 2015).

1.2 Diagnostic features of Annonaceae family

The Annonaceae family is readily identified by a suite of morphological and anatomical traits that serve as reliable diagnostic features across its taxa. Members of the family are predominantly aromatic trees, shrubs, or, less commonly, lianas, often with lenticellate stems and simple, alternate, distichous leaves (except *Tetrameranthus*) that lack stipules and exhibit entire margins and brochidodromous or campylodromous venation (Maas et al., 2007; Maas et al., 2015). When cut, many species emit a characteristic odor, and their indumentum may consist of simple, scale-like, or stellate trichomes (Leboeuf et al., 1980; Maas et al., 2007; Maas et al., 2015). Flowers are typically axillary or extra-axillary, rarely terminal, oppositifolious, mostly bracteate, and occur singly or in rhipidiate inflorescences. The pedicels are usually articulated at the base, except in *Guatteria*. Flowers are bisexual, rarely androdioecious, and actinomorphic, with differentiated perianth parts. Sepals are free or variously connate and arranged in valvate or imbricate aestivation (Leboeuf et al., 1980; Maas et al., 2007; Maas et al., 2015). Petals are usually 6, though sometimes 3, 4, 8, or 12, typically arranged in whorls, subequal to markedly unequal, free or rarely connate, valvate or imbricate, and generally fleshy or thickened. Stamens are few too numerous, spirally arranged, free, and connective, often with a shield-like apical prolongation; anthers are longitudinally dehiscent and may be locellate or not; staminodes are rarely present. Carpels are few too many, free or fused at the base, and rarely completely connate. The ovary is superior, with carpels usually numerous, rarely few, and ovules 1 to many, either basal or parietal (Leboeuf et al., 1980; Maas et al., 2007; Maas et al., 2015). Fruits are mostly apocarpous, formed by free, often stipitate, generally indehiscent monocarps, although syncarpous and dehiscent fruits also occur, particularly in genera such as *Annona* (Maas et al., 2007). Seeds are often large, sometimes arillate, and characteristically possess a ruminate endosperm with a minute embryo, a feature also shared with the related Myristicaceae (Maas et al., 2007). Additional diagnostic features include the presence of resin canals and septate piths, which are associated with the production of aromatic compounds and ecological interactions (Leboeuf et al., 1980). These combined characteristics aid in taxonomic identification and underscore the family's phylogenetic position among basal angiosperms.

1.3 Economic importance and traditional uses of Annonaceae family

The economic value of the Annonaceae family is substantial, primarily due to its fruit-bearing species, which hold significant commercial and nutritional importance. Among its genera, only *Annona* and *Asimina* stand out for producing economically important edible fruits. Notable species within *Annona* include *A. cherimola* Mill. (cherimoya), *A. squamosa* L. (sugar apple or sweetsop), *A. muricata* L. (soursop), the hybrid *A. cherimola* × *A. squamosa* (atemoya), *A. diversifolia* Saff. (ilama), *A. reticulata* L. (Bullock's heart), *A. glabra* L. (pond apple), and *A. purpurea* Moc. and Sessé ex Dunal (soncoya), while *A. triloba* L. (pawpaw) is the sole economically relevant species in the genus *Asimina* (Hernández Fuentes et al., 2021; Al Kazman et al., 2022). Regarding production value, it was estimated that in Brazil, only in 2017, the fruits of *A. squamosa*, *A. muricata*, and the hybrid *A. cherimola* × *A. squamosa* had a combined production value exceeding 65 million reais (IBGE, 2024). Although these fruits are predominantly consumed in their fresh form, they are also subject to industrial processing and commercialization in diverse value-added products, such as alcoholic formulations, desserts, dehydrated flakes, ice creams, jams, jellies, juices, milk-based beverages, nectars, syrups, yogurts, and extracts enriched with bioactive compounds exhibiting medicinal properties. (Hernández Fuentes et al., 2021).

Regarding the medicinal properties of Annonaceae, their value is well documented across tropical and subtropical regions, where Indigenous peoples and local communities have traditionally used these plants for medicinal and cultural purposes (Silva et al., 2018a; Silva et al., 2018b; Leite et al., 2020; Mohanty et al., 2023; Mouafon et al., 2025). For *Annona* species, the most frequent use is for the treatment of gastrointestinal tract diseases, skin diseases, respiratory system diseases, diabetes, and snakebite treatments, among others. However, it has also been used for the treatment of diseases caused by infectious agents such as malaria and Ebola, as well as for cancer treatment or prevention (Leite et al., 2020; Al Kazman et al., 2022). Similarly, *Duguetia* species have a long history in traditional medicine and are associated with a wide range of reported biological activities, including anticancer, anti-inflammatory, antimicrobial, antimalarial, antinociceptive, antioxidant, antiparasitic (antiprotozoal, antiplasmodial, leishmanicidal, trypanocidal), antirheumatic, and insecticidal properties (Mouafon et al., 2025). Species of *Uvaria*, in turn, have been traditionally used to treat diseases such as diabetes, epilepsy, fever, jaundice, malaria, menstrual pain, and minor infections (Mohanty et al., 2023). Similarly, *Unonopsis* species are widely used in the treatment of conditions such as arthritis, bronchitis, rheumatism, diarrhea, malaria, and age-related cognitive disorders (Silva et al., 2018a; Silva et al., 2018b). In general, preparation methods involving Annonaceae species vary considerably, ranging from decoctions and infusions of leaves, bark, or roots to topical applications, highlighting the importance of traditional knowledge in guiding therapeutic practices (Leite et al., 2020). In this context, ethnobotanical surveys further underscore the global relevance of this traditional knowledge, particularly in India, Africa, South America, and Southeast Asia, where local populations continue to make extensive use of Annonaceae species in folk

medicine (Focho et al., 2010; Frausin et al., 2014; Mohanty et al., 2023).

Pharmacological studies have corroborated traditional claims, demonstrating activities such as antidiabetic, anticancer, antipyretic, antimicrobial, antioxidant, and anti-inflammatory effects across various species (Leite et al., 2020; Al Kazman et al., 2022; Mohanty et al., 2023; Christopher, 2022). These pharmacological properties are attributed to the complex chemical profiles of Annonaceae plants, often involving synergistic interactions between multiple secondary metabolites (Leite et al., 2020). However, most pharmacological investigations have focused on limited species and chemical classes, with many species remaining unexplored. This gap highlights the urgent need for integrated approaches combining ethnobotanical surveys, phytochemical analyses, and bioassays to fully exploit the therapeutic potential of Annonaceae biodiversity.

1.4 Phytochemistry of Annonaceae family

The chemical diversity within Annonaceae is remarkable, encompassing a wide array of primary and secondary metabolites. Regarding primary metabolites, carbohydrates, lipids, amino acids, and proteins have been reported (Leboeuf et al., 1980). On the other hand, alkaloids represent the most extensively studied class of secondary metabolites, constituting approximately 76% of identified metabolites in genera such as *Duguetia* (Leboeuf et al., 1980; Mouafon et al., 2025). Almost all these alkaloids possess an isoquinoline-derived structure and are divided into subclasses such as simple isoquinolines, benzyltetrahydroisoquinolines, bisbenzylisoquinolines, bisbenzyltetrahydroisoquinolines, protoberberines, tetrahydroprotoberberines, and aporphinoids. On the other hand, aporphinoids can be divided into several subclasses, such as aporphines, oxoaporphines, C-7 and/or C-4 substituted aporphines, dehydroaporphines, phenanthrenes, and miscellaneous isoquinoline-type alkaloids. Aporphines, in turn, include noraporphines, aporphines, quaternary aporphines, aporphine *N*-oxides, and natural *N*-acylated noraporphines (Leboeuf et al., 1980; Guinaudeau et al., 1994). In addition to alkaloids, Annonaceae species produce terpenoids, flavonoids, acetogenins, and miscellaneous compounds (Leboeuf et al., 1980). Terpenoids include diterpenoids such as xylopic acid isolated from *Xylopia aethiopica*, which has been the subject of early phytochemical research dating back to the 1950s (Moreira et al., 2013). Acetogenins are another important class known for potent cytotoxic and pesticidal properties, although they have been less explored comparatively (Leboeuf et al., 1980).

Although flavonoids are well-established as biologically active compounds across numerous plant families (Panche et al., 2016; Dias et al., 2021), their presence and diversity within Annonaceae have remained notably underexplored. Despite scattered reports confirming their occurrence in several genera, flavonoids have received far less scientific attention compared to the extensively studied alkaloids and acetogenins traditionally associated with this family. To date, no comprehensive investigation has systematically mapped the structural diversity, distribution, or biosynthetic significance of flavonoids across Annonaceae. A notable exception is the work of Santos and Salatino (2000), which focused on Brazilian species and reported 76 compounds, primarily flavonoid glycosides derived from flavones (e.g., apigenin, luteolin) and flavonols (e.g., kaempferol, quercetin, isorhamnetin), with a clear predominance of flavonol derivatives. While this study underscores the chemical relevance of flavonoids within the family, it also highlights the fragmented nature of current knowledge. The absence of a holistic survey leaves a critical gap in our understanding of how flavonoids contribute to the phytochemical landscape, biological potential, and evolutionary ecology of Annonaceae, a gap this review seeks to address.

2 Flavonoids and their derivatives from Annonaceae

2.1 General comments

The biosynthesis of flavonoids derives from the combination of two main metabolic pathways: the shikimate pathway and the acetate pathway (Figure 1). From the convergence of these routes, the characteristic C6-C3-C6 flavonoid backbone is formed (Chen et al., 2022). The shikimate pathway begins with the condensation of D-erythrose-4-phosphate and phosphoenolpyruvate (PEP), resulting in the formation of a series of intermediates that culminate in the synthesis of shikimic acid. This compound undergoes sequential reactions to be converted into chorismic acid. According to Nabavi et al. (2020), this conversion initially involves an ATP-dependent phosphorylation that yields shikimic acid-3-phosphate. Subsequently, an addition–elimination reaction with a second molecule of PEP occurs, resulting in 5-enolpyruvylshikimate-3-phosphate (EPSP). Finally, the conversion of EPSP into chorismic acid occurs through a 1,4-elimination reaction, which releases a molecule of phosphoric acid. Thus, chorismic acid is the direct precursor of the aromatic amino acids L-phenylalanine and L-tyrosine, which are formed through decarboxylation and aromatization reactions. These aromatic amino acids undergo deamination, leading to the formation of hydroxycinnamic acids, such as p-coumaric acid, which is subsequently activated by a CoA ligase to generate 4-hydroxycinnamoyl-CoA (Cheng et al., 2014).

Simultaneously, the acetate pathway produces malonyl-CoA units from acetyl-CoA through the action of acetyl-CoA carboxylase. Three malonyl-CoA units condense with one 4-hydroxycinnamoyl-CoA unit in a reaction catalyzed by chalcone synthase, forming a polyketide intermediate. Through a Claisen-type condensation reaction, the compound naringenin chalcone forms the first intermediate with the basic structure of a flavonoid (Nabavi et al., 2020).

Naringenin chalcone can follow two distinct pathways. In one of them, a H_2 addition occurs at carbons 7 and 8, forming a dihydrochalcone known as naringenin dihydrochalcone. Dihydrochalcones comprise a flavonoid subclass characterized by the absence of a cyclized C-ring, which confers greater structural flexibility. In the other pathway, a cyclization catalyzed by the enzyme chalcone isomerase occurs via a Michael-type nucleophilic attack of the hydroxyl group on the α,β-unsaturated ketone, resulting in the formation of the flavanone naringenin (Lin et al., 2021). Flavanones have a saturated C-ring and represent key intermediates in the biosynthesis of three flavonoid subclasses.

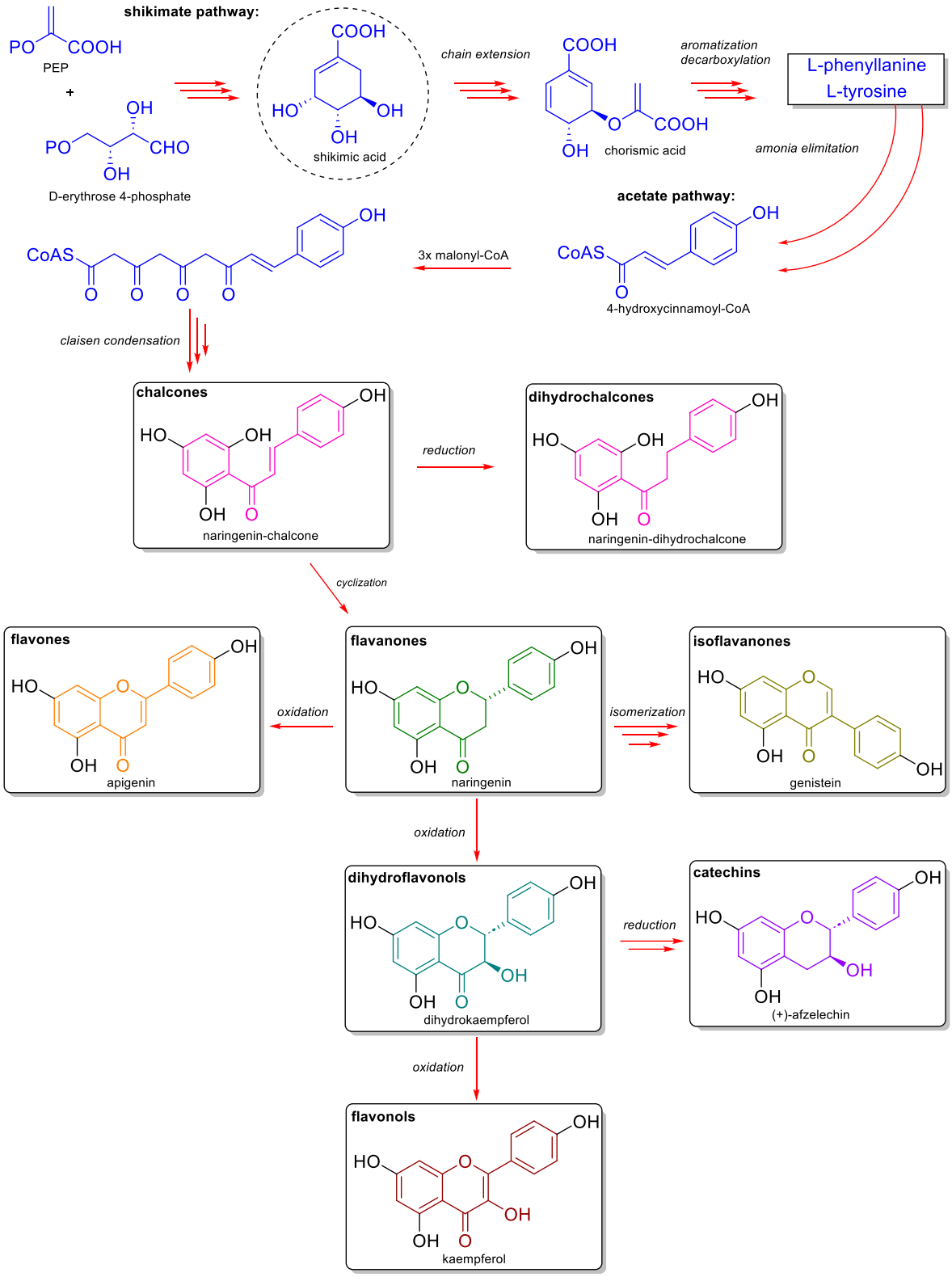

FIGURE 1
Biosynthetic pathway of flavonoids. The path begins with the shikimate route, which produces the aromatic amino acids L-phenylalanine and L-tyrosine—precursors in the formation of cinnamic acid and its derivatives. The condensation of 4-coumaroyl-CoA with three units of malonyl-CoA gives rise to chalcones, which are central intermediates in flavonoid biosynthesis. From chalcones, various enzymatic modifications—such as reduction, cyclization, isomerization, and oxidation—lead to the formation of the main flavonoid subclasses: flavanones (e.g., naringenin), flavones (e.g., apigenin), isoflavones (e.g., genistein), dihydroflavonols (e.g., dihydrokaempferol), catechins (e.g., (+)-epicatechin), and flavonols (e.g., kaempferol).

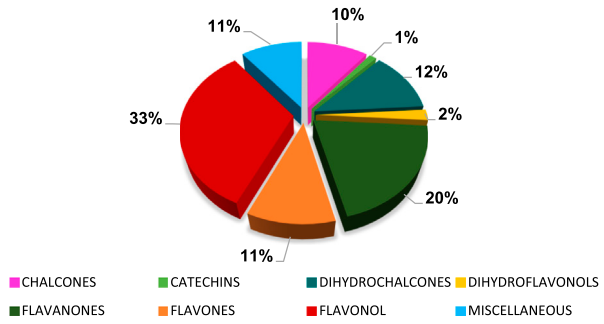

FIGURE 2
The graph shows the relative proportion of flavonoid subclasses reported in species of the Annonaceae family, including chalcones, dihydrochalcones, flavanones, flavonols, flavones, catechins, dihydroflavonols, and other miscellaneous compounds.

Through oxidation catalyzed by the enzyme flavone synthase, naringenin is converted into apigenin, a flavone characterized by a double bond between carbons 2 and 3 of the central (C) ring (Liu et al., 2021). Through a radical oxidation, followed by a 1,2-aryl migration and dehydration—reactions catalyzed by 2-hydroxyisoflavanone synthase and 2-hydroxyisoflavanone dehydratase—naringenin is also converted into the isoflavone genistein (Bosse et al., 2021). Isoflavones are distinguished by the B-ring being relocated from position 2 to position 3 of the C-ring. Naringenin may also undergo hydroxylation at position C-3 by the enzyme flavanone 3-hydroxylase, forming dihydrokaempferol, a member of the dihydroflavonol class (Liu et al., 2021). Dihydroflavonols are important biosynthetic intermediates, with a saturated C-ring and a hydroxyl group at position 3.

Dihydrokaempferol can also follow two distinct biosynthetic routes. In one pathway, a dehydrogenation reaction at carbons 2 and 3, catalyzed by the enzyme flavonol synthase, leads to the formation of kaempferol, a flavonol (Meng et al., 2019). Flavonols are characterized by the presence of a C2–C3 double bond and a hydroxyl group at C3, and they are among the most abundant flavonoids in nature, exhibiting diverse biological activities. In the alternative pathway, the reduction of dihydrokaempferol, catalyzed by dihydroflavonol 4-reductase and leucoanthocyanidin reductase, results in the formation of catechins, such as (+)-afzelechin (Raza et al., 2024). Catechins belong to the flavan-3-ol class, compounds that lack a double bond in the C-ring but possess a hydroxyl group at the C-3 position.

The diversity of flavonoids identified in the Annonaceae family can be seen in Figure 2, which shows the proportional distribution of the subclasses that will be described below. Flavonols and flavanones are the most abundant subclasses, followed by chalcones and dihydrochalcones. Flavones, catechins, dihydroflavonols, and miscellaneuos appear in smaller proportions.

Therefore, Figure 3 shows the geographical distribution of flavonoids isolated from species of the Annonaceae family, as well as the genera associated with each country. There is a clear predominance of studies conducted in Asia, especially in Thailand and Vietnam, which account for the largest number of described compounds and encompass a wide diversity of genera. To a lesser extent, African countries such as Nigeria, Cameroon, and Tanzania also stand out for their contribution of species with phytochemical relevance. The Americas, in turn, show more sporadic records, mainly in Brazil and Mexico. This distribution highlights a strong geographical bias in the investigations, reflecting both the floristic richness of tropical regions and the concentration of active research groups in these areas.

2.2 Chalcones

For chalcones, 25 structures (Figure 4) were isolated from various plant species, predominantly from the genera *Melodorum*, *Friesodielsia*, *Fissistigma*, *Uvaria*, and *Desmos*, mainly collected in Southeast Asia and Africa, including countries such as Thailand, Vietnam, Sri Lanka, and Cameroon. These chalcones were obtained from different plant parts, including leaves, fruits, roots, stems, and aerial parts, highlighting their wide distribution within plant tissues. The isolated compounds exhibit significant structural diversity, particularly in the substitution patterns of hydroxy, methoxy, and benzyl groups. Biologically, many of these chalcones demonstrated noteworthy anti-inflammatory, antioxidant, antimicrobial, antiplasmodial, and cytotoxic activities, underlining their potential as promising pharmacological agents. The following sections detail the chemical features and biological activities of each identified compound.

Flavokawain-A (**1**) and 2′,4′-dihydroxy-4,6′-dimethoxychalcone (**2**) were isolated from the aerial parts of *Goniothalamus gardneri* (collected in Sri Lanka) (Seidel et al., 2000). Later, Chan et al. (2013) investigated the anti-inflammatory activity of **1** and observed its ability to inhibit superoxide anions, with a half maximal inhibitory concentration (IC_{50}) of 8.65 μM, as well as modest elastase inhibitory activity. Furthermore, compound **2** exhibited inhibition of Interleukin-8 (IL-8) (a chemokine involved in the inflammatory response) production with an IC_{50} of 8.6 μM and inhibited tumor necrosis factor alpha (TNF-α) production in lipopolysaccharide (LPS) stimulated human neutrophils with an IC_{50} of 13.3 μM (Engels et al., 2018). Additional chalcones with a similar substitution pattern, specifically 4,4′-dihydroxy-2′,6′-dimethoxychalcone (**3**) and helichrysetin (**4**), were isolated from the fruits of *Melodorum siamensis* collected in Thailand (Jaidee et al., 2019). Besides, Ngoc et al. (2019) isolated the compound 2-hydroxy-3,4,5,6-tetramethoxychalcone (**5**) from the stem of *Fissistigma polyanthoides* from Vietnam. This compound features a B-ring fully substituted with four methoxy groups and one hydroxy group. Additionally, compound **5** demonstrated antioxidant activity by inhibiting the formation of intracellular reactive oxygen species (ROS) in human bronchial epithelial cell line (BEAS-2B) cells treated with 2,2′-Azobis(2-amidinopropane) dihydrochloride (AAPH), with an IC_{50} value of 59.9 μM.

The compound cardamonin (**6**), isolated from the leaves of *Desmos cochinchinensis* (from Thailand), displayed no substitution at ring B and exhibited potent antioxidant activity and moderate cytotoxicity (Bajgai et al., 2011). Additionally, a study conducted by Meesakul et al. (2017) showed that this compound exhibited an

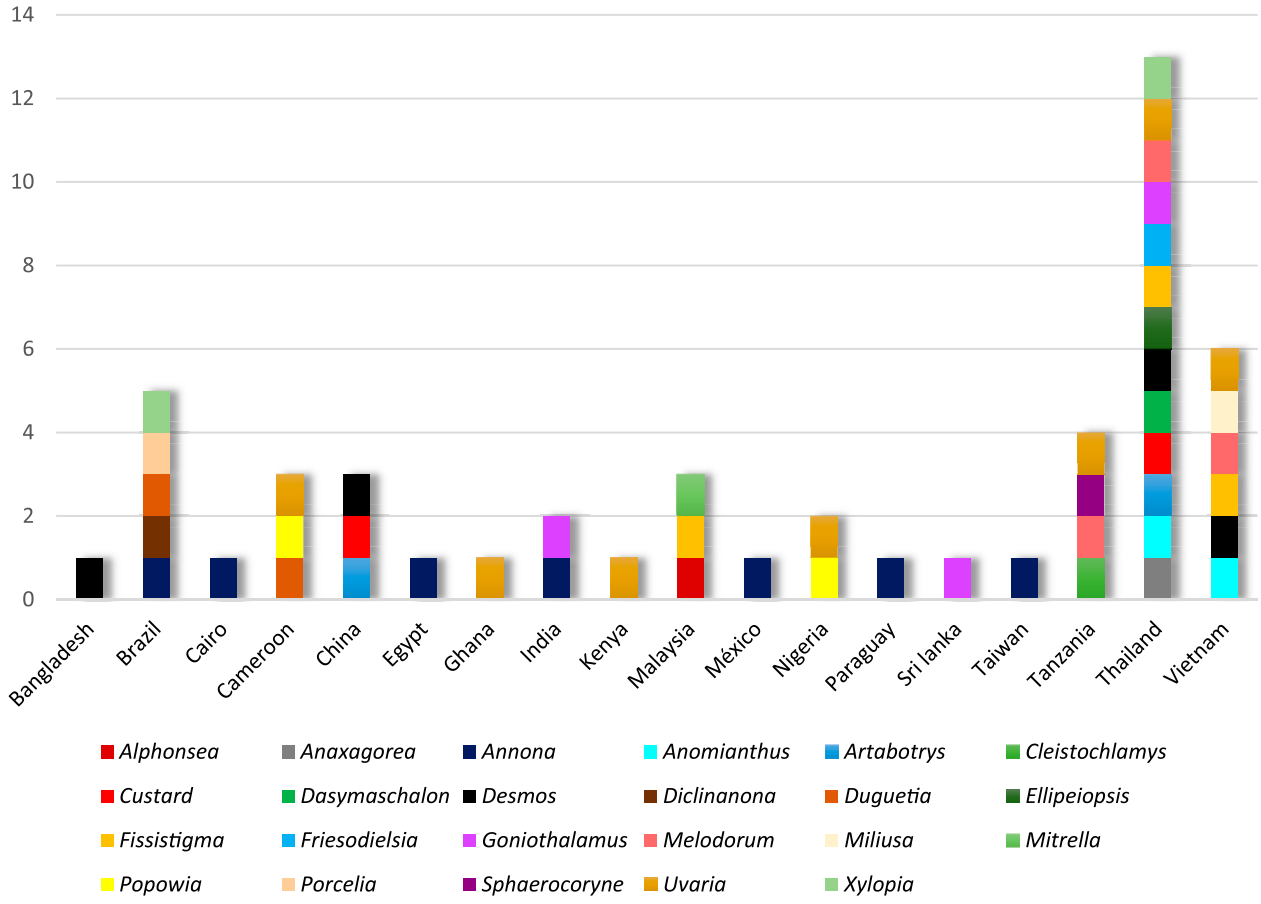

FIGURE 3
Distribution of flavonoids isolated from species of the Annonaceae family in different countries, also indicating the most representative genera in each region.

inhibitory effect on nitric oxide (NO) production with an IC_{50} of 28.14 μM. The compound 2′,4′-dihydroxy-3′,6′-dimethoxychalcone (**7**) was isolated from the leaves of *Friesodielsia desmoides* and demonstrated an inhibitory effect on NO production with an IC_{50} = 37.21 μM. Furthermore, the aldehyde derivative 3′-formyl-2′,4′-dihydroxy-6′-methoxychalcone (**8**) was isolated from the leaves of *Friesodielsia discolor*, collected in Thailand (Prawat et al., 2012). Interestingly, compound **8** exhibited antiplasmodial activity against *Plasmodium falciparum* (IC_{50} = 2.75 μg/mL), antimicrobial activity against *Mycobacterium tuberculosis* was observed, with a minimum inhibitory concentration (MIC) of 6.25 μg/mL and cytotoxic activity against the epidermoid carcinoma in the mouth (KB) with an IC_{50} of 6.50 μg/mL and the human breast adenocarcinoma (MCF-7), with an IC_{50} value of 4.13 μg/mL. The compound 2′,6′-dihydroxy-4′-methoxychalcone (**9**), isolated from the leaves of *Melodorum fruticosum* (from Vietnam), showed inhibition of IL-8 production with an IC_{50} = 11.6 μM and inhibition of TNF-α production in LPS stimulated human neutrophils with an IC_{50} = 6.2 μM (Engels et al., 2018). Additionaly, the compound 2′,3′-dihydroxy-4′,6′-dimethoxychalcone (**10**) was isolated from the leaves of *Anomianthus dulcis* collected in Thailand and no bioactivity was observed (Sinz et al., 1999).

The compound pedicin (**11**) was isolated from the leaves of *Fissistigma lanuginosum* (from Malaysia) (Alias et al., 1995), displaying the ring A fully substituted with three methoxy and two hydroxy groups. Besides, kanakugiol (**12**), isolated from the fruits of *Popowia cauliflora*, (from Cameroon) differs from **11** by containing four methoxy groups and one hydroxy group at the ring A (Waterman and Pootakahm, 1979). From the same plant, the additional chalcones 2′-hydroxy-3′,4′,6′-trimethoxychalcone (**13**), 2′,3′,4′,6′-tetramethoxychalcone (**14**), and 2′,4-dihydroxy-3′,4′,6′-trimethoxychalcone (**15**) were isolated (Waterman and Pootakahm, 1979). On the other hand, melosiamensone E (**16**), obtained from the leaves of *Melodorum siamensis* collected in Thailand, features a quinone core bearing three methoxy groups in ring B (Jaidee et al., 2019). The compound 2-hydroxy-3,4,6-trimethoxychalcone (**17**), isolated from the roots of *Uvaria dependens* (Tanzania) (Nkunya et al., 1993b), exhibited cytotoxic activity against human promyelocytic leukemia cells (HL-60) with an IC_{50} of 22.9 μM (Moriyasu et al. (2011). From leaves of *Melodorum fruticosum* (from Vietnam), discovered the

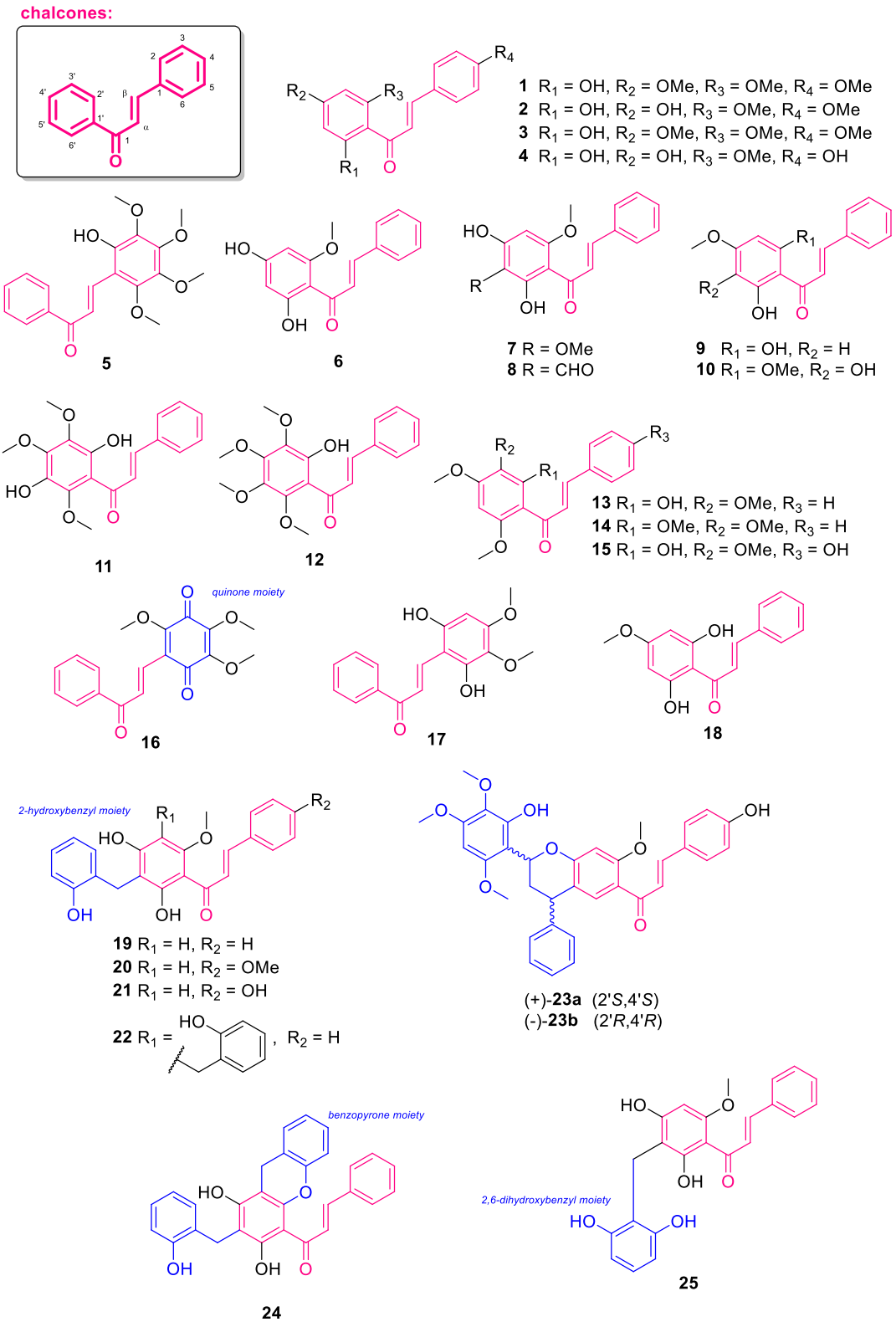

FIGURE 4
Chemical structures of chalcones isolated from Annonaceae (**1**–**25**).

compound 2′,6′-dihydroxy-4′-methoxychalcone (**18**), which showed potential anti-inflammatory activity by inhibiting superoxide anions, with an IC_{50} value of 8.40 μM (Chan et al., 2013).

From the leaves of *Ellipeiopsis cherrevensis* collected in Thailand, the molecule 2′,4′-dihydroxy-3′-(2-hydroxybenzyl)-6′-methoxychalcone (**19**) was isolated (Wirasathien et al., 2006). Compound **19** showed cytotoxic activity against human tumor cell lines human small cell lung carcinoma (NCI-H187), KB, and breast cancer (BC), with IC_{50} values of 1.40, 5.31, and 13.92 μg/mL, respectively (Wirasathien et al., 2006). Also, **19** exhibited antimalarial activity against *Pasmodium falciparum*, with an IC_{50} = 7.1 μg/mL and antimicrobial activity against *Mycobacterium tuberculosis* (MIC = 25 μg/mL) (Wirasathien et al., 2006). In another study, **19** compound also exhibited cytotoxic activity against KB, MCF-7, and NCI-H187 cell lines, with IC_{50} values of 1.26, 2.08, and 3.98 μg/mL, respectively (Lekphrom et al., 2018). The compound 2′,4′-dihydroxy-3′-(2-hydroxybenzyl)-4,6′-dimethoxychalcone (**20**) was isolated from the leaves of *Melodorum fruticosum* (Engels et al., 2018). This compound is structurally similar to **19**, as both feature a hydroxybenzyl group on the A-ring but differ by the presence of a methoxy group on the B-ring in **20**.

The compounds cherrevenones B (**21**) and C (**22**) were isolated from the fruits of *Uvaria cherrevensis*, from Thailand (Auranwiwat et al., 2018). Compound **21** is the first example of this review that displays the presence of a hydroxybenzyl connected to ring A. Alternatively, **22** contains two hydroxybenzyl groups attached at C-3′ and C-5'. Compound **21** exhibited cytotoxic activity against KB and African green monkey kidney epithelial (Vero) cell lines, with IC_{50} values of 2.76 and 3.34 μM, respectively, while **22** displayed moderate inhibitory activity against the K1CB1 strain of *Plasmodium falciparum* (a chloroquine- and pyrimethamine-resistant strain) (IC_{50} = 43.5 μM) (Auranwiwat et al., 2018). The molecules (−)-melosiamensone A (**23a**) and (+)-melosiamensone A (**23b**) were isolated as an enantiomeric mixture from the fruits of *Melodorum fruticosum* (Jaidee et al., 2019). These compounds display an uncommon chalcone-phenylpropanoid hybrid structure that the authors speculate to be formed via a Michael addiction-like reaction. Their absolute configurations were determined as (2′*S*,4′*S*) and (2′*R*,4′*R*), respectively, based on chiral reverse-phase liquid chromatography purification and Electronic Circular Dichroism (ECD) analysis with aid of theoretical calculations. On the other hand, cherrevenone A (**24**), obtained from fruits of *Uvaria cherrevensis* exhibited a benzopyrone moiety fused with the A-ring at positions C-2′ and C-3' (Auranwiwat et al., 2018). Moreover, **24** displayed an IC_{50} of 21.0 μM against the Tm4/8.2 (a chloroquine-sensitive strain) and K1CB1 strains of *P. falciparum*, as well as cytotoxic activity against KB and Vero cells, with IC_{50} values of 0.60 and 0.61 μM, respectively (Auranwiwat et al., 2018). Additionally, the compound 2′,4′-dihydroxy-3′-(2,6-dihydroxybenzyl)-6′-methoxychalcone (**25**) was isolated from the leaves of *Desmos chinensis* collected in Bangladesh (Rahman et al., 2003). Interestingly, **25** features a 2,6-dihydroxybenzyl substituent attached to the B-ring of the chalcone skeleton.

2.3 Dihydrochalcones

About dihydrochalcones, 29 structures (Figure 5) were isolated from various plant species, with notable representation from the genera *Uvaria*, *Melodorum*, *Fissistigma*, and *Miliusa*, predominantly collected in Southeast Asia and parts of Africa. These compounds were extracted from diverse plant parts, including roots, leaves, stems, twigs, and aerial portions. The isolated dihydrochalcones display a wide range of substitution patterns, including fully substituted aromatic rings, β-substituted variants (such as β-methoxy and β-ethoxy derivatives), and rare benzopyrone-fused skeletons. Several of these compounds exhibit significant biological activities, including cytotoxicity, antimicrobial effects, and inhibitory effects on the nuclear factor of activated T-cells (NFAT), as well as selective activity against human tumor cell lines and *Mycobacterium* species. In addition, several dihydrochalcones bearing hydroxybenzyl or 2-(4-hydroxyphenethyl)phenol moieties further enrich the chemical diversity observed within this class. The following section provides a detailed overview of their structures, sources, and reported bioactivities.

The compounds dihydropashanone (**26**) and 2′,6′-dihydroxy-4′-methoxydihydrochalcone (**27**) were isolated from the twigs and leaves of *Miliusa balansae*, collected in Vietnam (Kamperdick et al., 2002). To add to that, compounds 2-hydroxy-3′,4′,6′-trimethoxydihydrochalcone (**28**), 2′-hydroxy-3′,4′,6′-trimethoxydihydrochalcone (**29**), 2′-hydroxy-3′,4′,6′-trimethoxy-β′-methoxychalcane (**30**) and 2′-hydroxy-3′,4′,6′-trimethoxy-β′-ethoxychalcone (**31**) were isolated from the leaves of *Fissistigma bracteolatum*, also from Vietnam (Lien et al., 2000). Compounds **30** and **31** do not display the common β-keto group from other dihydrochalcones, instead this function was replaced by a methoxy and an ethoxy group, respectively. From the leaves of *Anomianthus dulcis* (collected in Thailand), the compound 2′,3′-dihydroxy-4′,6′-dimethoxydihydrochalcone (**32**) was isolated (Sinz et al., 1999). Further investigation displayed an inhibitory activity of 32 against the NFAT transcription factor, with an IC_{50} of 9.77 μM (Kiem et al., 2005). Additional dihydrochalcones were isolated from the leaves of *Melodorum siamensis* and named melosiamensone F (**33**) and 4′,4-dihydroxy-2′,6′-dimethoxydihydrochalcone (**36**) (Jaidee et al., 2019).

The compounds **34** (2-hydroxy-3,4,5,6-tetramethoxydihydrochalcone) (Ngoc et al., 2019) and **35** (2′,5′-dihydroxy-3′,4′,6′-trimethoxydihydrochalcone) (Alias et al., 1995) were isolated by the species *Fissistigma polyanthoides* and *Fissistigma lanuginosum*, respectively. Compound **34** display the ring B fully substituted, while **35** present a fully substituted ring A. Moreover, uvangoletin (**37**) was obtained from the roots of *Uvaria angolensis*, collected in Nigeria (Hufford and Oguntimein, 1982). From the aerial parts of *Goniothalamus gardneri* (from Sri Lanka), the compounds 2′,4′-dihydroxy-4,6′-dimethoxydihydrochalcone (**38**) and 2′,4,4′-trihydroxy-6′-methoxydihydrochalcone (**39**) were isolated. These compounds exhibited cytotoxic activity against KB, MCF-7, and NCI-H187 cell lines, with IC_{50} values of 9.09, 16.72, and 14.26 μM for compound **38**, and 5.18, 10.92, and 8.82 μM for compound **39**, respectively (Prawat et al., 2013).

From the roots of a Nigerian specimen of *Uvaria angolensis*, angoletin (**40**) and anguvetin (**41**) were isolated (Hufford and Oguntimein, 1982). Both exhibited antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Mycobacterium smegmatis* with IC_{50} values of 12.5, 0.8, and 6.3 μM, respectively for **40** and 1.5, 0.2, and 1.5 μM, respectively for **41**. Additionally, the compound melosiamensone D (**42**) was isolated from the leaves of

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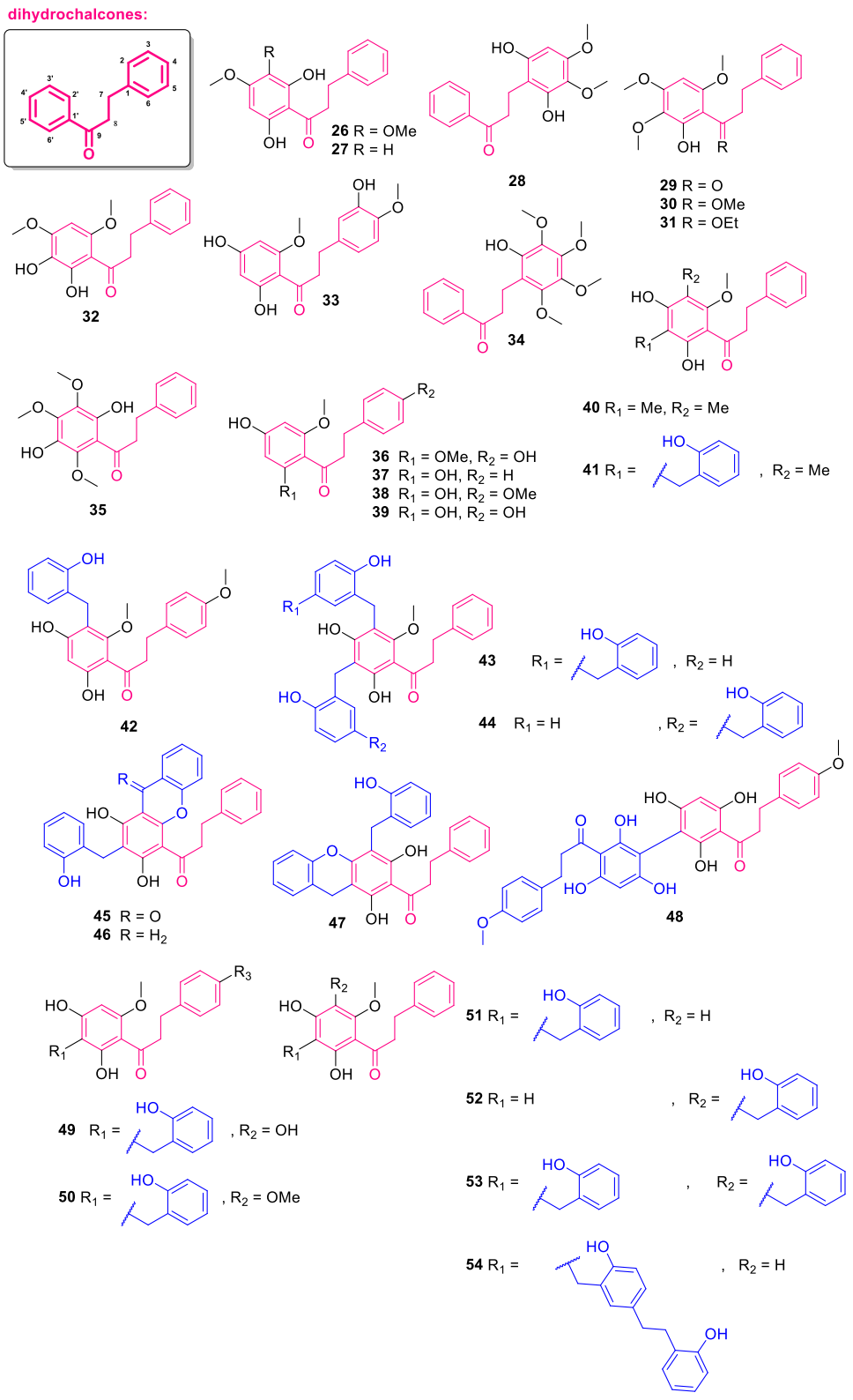

FIGURE 5
Chemical structures of dihydrochalcones isolated from Annonaceae (**26**–**54**).

Melodorum siamensis (Jaidee et al., 2019). By studying the roots of *Uvaria leptocladon*, collected in Thailand, Nkunya et al. (1993a) isolated two *C*-benzylated dihydrochalcones: triuvaretin (**43**) and isotriuvaretin (**44**). These two compounds possess a distinct substitution pattern at ring B, in which a 2-(4-hydroxyphenethyl) phenol-like group is the substituent at C-3′ and C-5′ for **43** and **44**,

respectively. Beyond, from the roots of *Uvaria acuminata*, collected in Kenya, the compounds isochamuvaretin (**45**) and acumitin (**46**), in both compounds a fused benzopyrone moiety as observed for **24** (Ichimaru et al., 2004). Both **45** and **46** exhibited cytotoxic activity against HL-60 human promyelocytic leukemia cells, with IC_{50} values of 8.2 and 4.1 μM, respectively.

The compound chamuvaretin (**47**) was isolated from the roots of *Uvaria chamae*, which displayed an interesting benzopyrone moiety fused to ring B at C-4′ and C-5' (Okorie, 1977). From the leaves of *Melodorum siamensis*, collected in Thailand, the chalcone dimer 3′,3″-bis-[2′,4′,6′-trihydroxy-4-methoxydihydrochalcone] (**48**) was isolated (Prawat et al., 2013). Additional dihydrochalcones named 2′,4,4′-trihydroxy-6′-methoxy-3′-(2″-hydroxybenzyl) dihydrochalcone (**49**) and 2′,4′-dihydroxy-4,6′-dimethoxy-3′-(2″-hydroxybenzyl)dihydrochalcone (**50**) were obtained from the leaves of *Melodorum siamensis* (Jaidee et al., 2019). Compound **49** exhibited IC_{50} values of 7.16, 14.86, and 3.66 μM against the KB, MCF-7, and NCI-H187 cell lines, respectively, while compound **50** showed IC_{50} values of 2.02, 20.03, and 2.73 μM against the same cell lines (Jaidee et al., 2019).

The compound uvaretin (**51**) was isolated from the roots of *Uvaria acuminata* by Cole et al. (1976). Then, Ichimaru et al. (2004) evaluated the cytotoxic potential of **51**, reporting an IC_{50} of 9.3 μM against HL-60 cells. Additionally, from the stem bark of *Uvaria chamae*, the compound isouvaretin (**52**) (also known as chamuvaretin) was isolated (Hufford and Lasswell, 1976). Compound **52** exhibited cytotoxic activity against HL-60 cells, with an IC_{50} value of 24.7 μM (Ichimaru et al., 2004). In the study conducted on the roots of *Uvaria angolensis*, Hufford and Oguntimein (1982) isolated the compound diuvaretin (**53**), which was further assayed and found to possess cytotoxic activity of this compound against HL-60 cells with an IC_{50} value of 6.1 μM (Ichimaru et al., 2004). Nkunya et al. (1993a), in a study with the roots of *Uvaria leptocladon*, (from Tanzania), isolated the compound angoluvarin (**54**). Compounds **51**–**53** bear variable patterns of substitution by 2-hydroxybenzil motifs, while **54** display an uncommon 2-(4-hydroxyphenethyl)phenol-like group attached to C-5'.

2.4 Flavanones

Concerning flavanones, 48 structures (Figures 6, 7) were isolated from a wide range of plant species belonging predominantly to the Annonaceae family, including genera such as *Melodorum*, *Uvaria*, *Desmos*, *Fissistigma*, and *Friesodielsia*. These compounds were obtained from various plant parts, including leaves, roots, stems, bark, twigs, and heartwood, mainly collected across Southeast Asia and West Africa. The isolated flavanones exhibit significant structural diversity, including diverse methoxy and hydroxy substitution patterns, formyl groups, and rare prenylated and C-benzylated derivatives. Several of these flavanones have been reported to exhibit potent biological activities, including antioxidant, cytotoxic, antiplasmodial, estrogenic, aromatase inhibitory, and α-glucosidase inhibitory properties. In particular, compounds featuring 2-hydroxybenzyl moieties, *O*-prenylation, and unusual dimeric or polybenzylated architectures stand out for their unique structures and promising bioactivity profiles. The following sections present these compounds in detail, highlighting their natural sources, structural characteristics, and biological evaluations.

The compound naringenin (**55**) was isolated from the heartwood of *Anaxagorea luzonensis*, collected in Thailand (Sabphon et al., 2015), while the compound (2*S*)-4′,5,7-trimethoxyflavanone (**56**) was isolated from the leaves of *Melodorum fruticosum*, collected in Vietnam (Engels et al., 2018). Moreover, the investigation of leaves of *Melodorum fruticosum* afforded the compound 4′,7-dihydroxy-5-methoxyflavanone (**57**). Compound **57** exhibited a superoxide anion inhibition activity with IC_{50} = 2.20 μM. Additionally, **57** also showed cytotoxic activity against KB and NCI-H187 cell lines, with IC_{50} values of 17.45 and 16.97 μg/mL, respectively (Chan et al., 2013).

The compound 4′-hydroxy-5,7-dimethoxyflavanone (**58**) was isolated from the leaves of *Melodorum fruticosum* (Engels et al., 2018). Tsugafolin (**59**) was isolated from the aerial parts of *Goniothalamus gardneri*, collected in India (Seidel et al., 2000). According to Chan et al. (2013), **58** exhibited superoxide anion inhibition with an IC_{50} = 2.50 μM. On the other hand, Prawat et al. (2013) demonstrated that this compound possesses cytotoxic activity against KB and NCI-H187 cell lines with IC_{50} values of 20.29 and 17.74 μg/mL, respectively. Furthermore, the compound 7-hydroxy-5-methoxyflavanone (**60**) was described from the leaves of *Melodorum fruticosum* (Engels et al., 2018) and pinostrobin (**61**) the stems of *Uvaria chamae* (Lasswell and Hufford, 1977). From the leaves and twigs of *Miliusa balansae* (collected in Vietnam), the compounds 5-hydroxy-4′,7-dimethoxyflavanone (**62**), 5-hydroxy-7,8-dimethoxyflavanone (**63**), and 5-hydroxy-6,7-dimethoxyflavanone (**64**) were isolated (Kamperdick et al., 2002). Besides, in the study conducted by Chan et al. (2013), the compound ponciretin (**65**) was isolated from the leaves of *Melodorum fruticosum* and showed a superoxide anion inhibition with an IC_{50} = 7.69 μM.

Additional flavanone analogues were isolated from Annonaceae plants, such as 5,7,8-trimethoxyflavanone (**66**) from the stems of *Popowia cauliflora* (from Nigeria) (Panichpol and Waterman, 1978), 8-hydroxy-5,7-dimethoxyflavanone (**67**) was isolated from the leaves of *Anomianthus dulcis* (from Thailand) (Sinz et al., 1999), 5-hydroxy-6,7,8-trimethoxyflavanone (**68**) from *Fissistigma polyanthoides* (from Vietnam) (Ngoc et al., 2019), naringenin trimethyl ether (**69**) from the aerial parts of *Goniothalamus gardneri* (from India) (Seidel et al., 2000), alpinetin (**70**) and 5,6,7-trihydroxyflavanone (**74**) from the leaves of *Friesodielsia desmoides* (from Thailand) (Meesakul et al., 2017), (+)-6,8-C-dimethylpinocembrin 5-methyl ether (**71**) and demethoxymatteucinol (**72**) from roots of *Uvaria angolensis* (from Nigeria) (Hufford and Oguntimein, 1982) and 5,6-dihydroxy-7-methoxyflavanone (**73**) from leaves of *Desmos chinensis* (from Vietnam) (Kiem et al., 2005).

The compound containing a formyl group at the C-8 position of the A-ring named 8-formyl-5,7-dihydroxyflavanone (**75**) was isolated from the leaves of *Friesodielsia discolor* (Prawat et al., 2012). An error in the carbon numbering of the structure is present in the original article, which refers to positions 4a and 8a instead of the correct ones, 5 and 10. Morevoer, the compound kanakugin (**76**) was isolated from the fruits of *Popowia cauliflora*, collected in Cameroon. Interestingly, this compound features an A-ring fully substituted with four methoxy groups (Waterman and

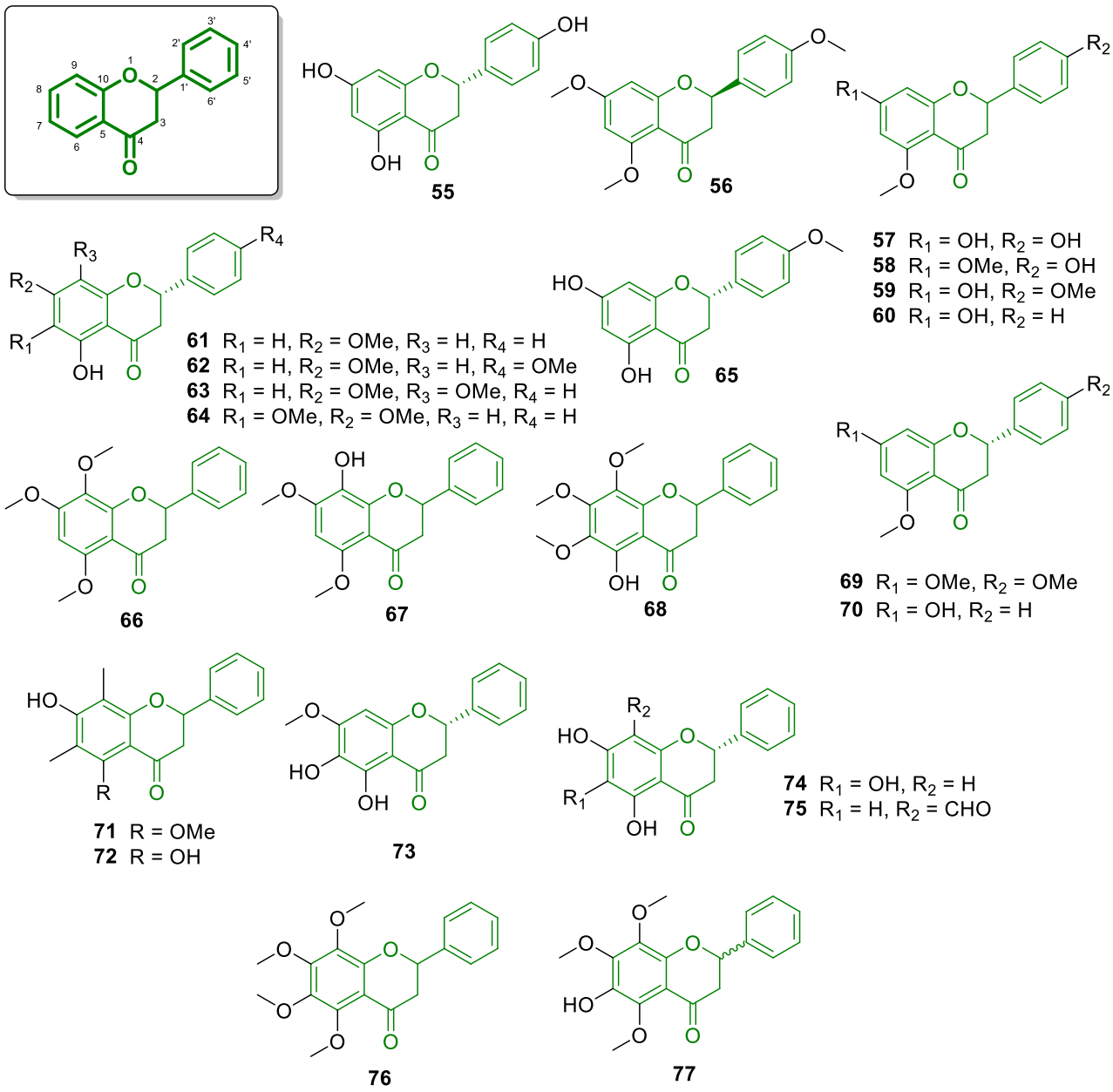

FIGURE 6
Chemical structures of flavanones isolated from Annonaceae (**55**–**77**).

Pootakahm, 1979). Furthermore, from the trunk barks of *Fissistigma oldhamii*, collected in Taiwan, was isolated the compound isopedicin (**77**) (Hwang et al., 2009). This molecule potently and concentration-dependently inhibited superoxide anion production in human neutrophils activated by formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP), with an IC_{50} value of 0.34 μM. In Vietnam, the stem barks of *Melodorum fruticosum* were collected and phytochemically studied to afford the molecules melodorone B (**78**), melodorone C (**79**), and onysilin (**80**) (Do and Sichaem, 2022). Compounds **78** and **79** are distinguished by the presence of *O*-prenyl groups at C-8 and C-7, respectively. Flavanones **78**–**80** were evaluated for their α-glucosidase inhibitory activity, displaying IC_{50} values of 3.33 μM (**78**), 4.00 μM (**79**), and 192 μM (**80**). Additionally, compounds **78** and **79** demonstrated cytotoxicity against KB (IC_{50} = 62.1 and 59.0 μM, respectively), human liver hepatocellular carcinoma (HepG2) (IC_{50} = 44.8 and 80.0 μM, respectively), and MCF-7 (IC_{50} = 73.7 μM, only for **78**) cell lines (Do and Sichaem, 2022).

Pinocembrin (**81**) was isolated from the stem of *Uvaria chamae* (from Ghana) (Lasswell and Hufford, 1977). Beyond, Bajgai et al. (2011), assayed this compound towards inhibition of the enzyme aromatase obtaining an IC_{50} value of 0.9 μM. In another study conducted by Meesakul et al. (2019), pinocembrin also inhibited the α-glucosidase enzyme with an IC_{50} value of 4.3 μM. The compounds

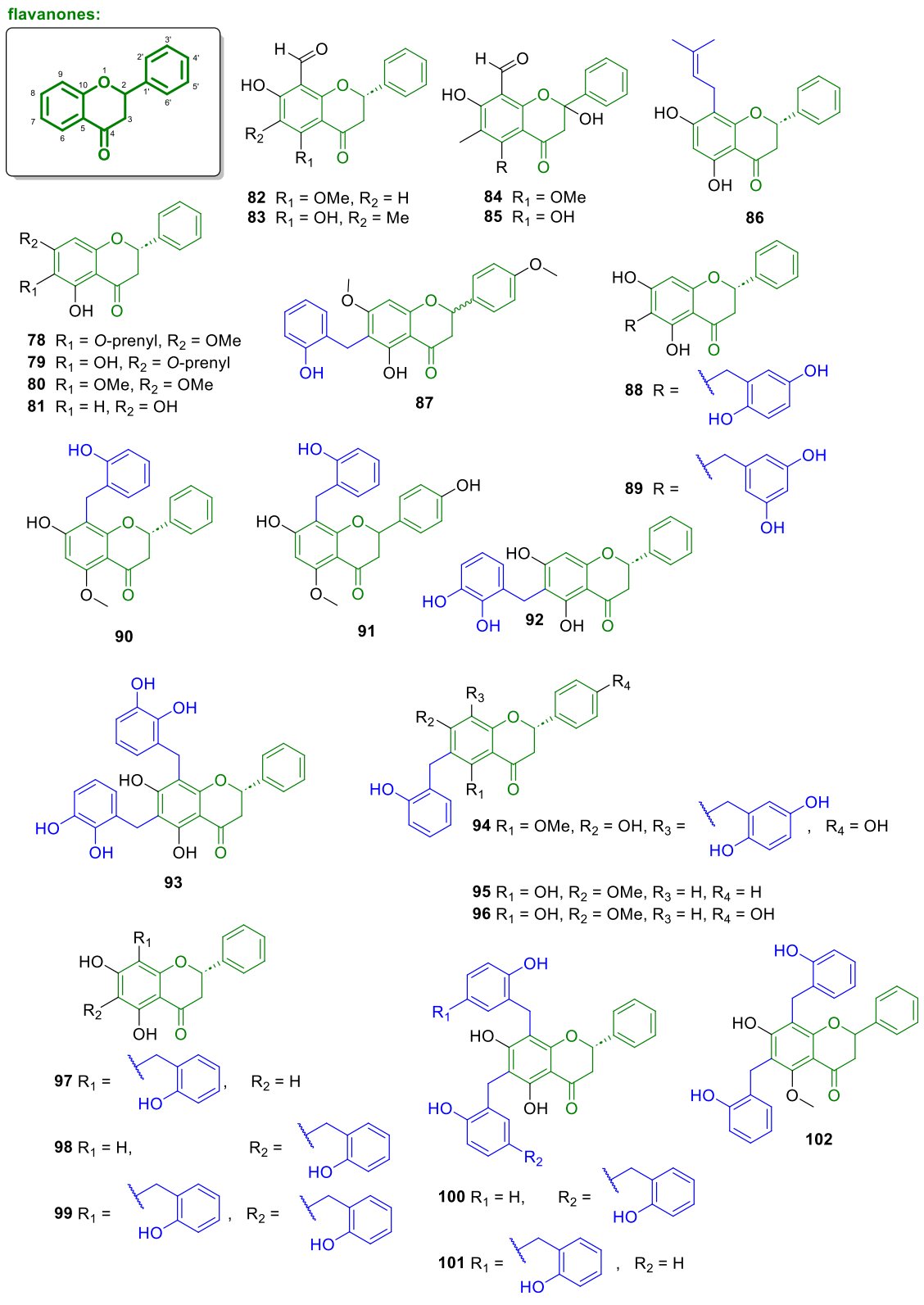

FIGURE 7
Chemical structures of flavanones isolated from Annonaceae (**82**–**102**).

8-formyl-7-hydroxy-5-methoxyflavanone (**82**) and lawinal (**83**) were isolated from the leaves of *Friesodielsia discolor* (Prawat et al., 2012). Compound **82** exhibited antiplasmodial activity against *Plasmodium falciparum* (IC_{50} = 2.78 μg/mL), antimicrobial activity against *Mycobacterium tuberculosis* (MIC = 25.00 μg/mL), and cytotoxic activity against KB (IC_{50} = 12.51 μg/

mL) and MCF-7 (IC_{50} = 10.27 μg/mL) cell lines. Desmosflavanone II (**84**) was isolated from the roots of *Desmos cochinchinensis* (from China) (Wu et al., 1997). Compound **84** displayed ring A is fully substituted with formyl, hydroxyl, methoxyl, and methyl groups. From the leaves and stems of *Desmos chinensis*, collected in Japan was isolated the flavanone desmal (**85**), which inhibited the growth of human epidermoid carcinoma cells (A431), retrovirus-transformed cell line (ER12), and rous sarcoma virus-transformed normal rat kidney cells (RSV'-NRK) (Kakeya et al., 1993).

The compound (2*S*)-8-isoperitenylnaringenin (**86**) was isolated from the heartwood of *Anaxagorea luzonensis* (from Thailand), exhibited strong estrogenic activity with an IC_{50} value of 140 nM (Kitaoka et al., 1998). The compound 5-hydroxy-6-(2-hydroxybenzyl)-4′,7-dimethoxyflavanone (**87**) was isolated from the leaves of *Melodorum fruticosum* (Engels et al., 2018). This compound is notable for containing a 2-hydroxybenzyl group at ring A, as also observed for chalcones and dihydrochalcones. Two compounds, (−)-(2*S*)-desmoscochinflavanones A (**88**) and B (**89**) were isolated from the twigs and leaves of *Desmos cochinchinensis*, (Meesakul et al., 2019). From the roots of *Uvaria angolensis*, was isolated the compound (±)-chamanetin 5-methyl ether (**90**) (Hufford and Oguntimein, 1982). Later, Lekphrom et al. (2018) described the cytotoxic activity against KB, MCF-7, and NCI-H187 cell lines of **90** with IC_{50} values of 42.37, 27.82, and 8.17 μg/mL, respectively.

Melosiamensone B (**91**), a flavone containing a 2-hydroxybenzyl at ring A, was isolated from the leaves of *Melodorum siamensis* (Jaidee et al., 2019). In the study by Maeda et al. (2020), the compounds 3″-hydroxyisochamanetin (**92**) and 3″-hydroxygracinol (**93**) were isolated from the leaves of *Sphaerocoryne gracilis*, collected in Tanzania. Both compounds exhibit (*S*)-configuration at C-2 of the C-ring. The compounds cherrevenone D (**94**), isochamanetin 7-methyl ether (**95**), and *epi*-methylphelligrin (**96**) were isolated from the fruits of *Uvaria cherrevensis* in Thailand, as described by Auranwiwat et al. (2018). All three compounds exhibit relative α-oriented ring C and a 2-hydroxybenzyl group at ring A. The compounds chamanetin (**97**), isochamanetin (**98**), and dichamanetin (**99**) were isolated from the stem of *Uvaria chamae* (Lasswell and Hufford, 1977). Compounds **97**–**99** exhibited cytotoxic activity against KB, human cervical cancer cells (HeLa), MCF-7, and HepG-2 cell lines (Hongnak et al., 2015). Compounds **98** and **99** also exhibited cytotoxic activity against NCI-H187 and Vero cell lines, with IC_{50} values of 40.28 and 19.31 μM for compound **98**, and 17.26 and 22.29 μM for compound **99** (Chokchaisiri et al., 2017). In the study by Costa et al. (2021), compound **98** exhibited cytotoxic activity against HepG2 and human lung fibroblast cell line (MRC-5) cell lines (IC_{50} = 19.79 and 24.69 μg/mL, respectively). In contrast, compound **99** was cytotoxic against HL-60, MCF-7, and human colorectal carcinoma cell line (HCT116) cell lines, with IC_{50} values of 15.78, 23.59, and 18.99 μg/mL, respectively.

In the work of Hufford et al. (1979), the compound uvarinol (**100**) was isolated from the stem of *Uvaria chamae*. This compound features two 2-hydroxybenzyl groups on the A-ring, one of which (at C-6) is further substituted with another 2-hydroxybenzyl group. The compound isouvarinol (**101**) was isolated from two *Uvaria* species, *U. lucida* and *U. doeringii* (Achenbach et al., 1997). This compound also possesses two 2-hydroxybenzyl groups on the A-ring, with the group at C-8 being substituted with an additional 2-hydroxybenzyl group. From the stem and root of *Uvaria cherrevensis*, (±)-dichamanetin 5-methyl ether (**102**) was isolated, which exhibited cytotoxic activity against the Vero cell line, with an IC_{50} = 38.6 μM (Auranwiwat et al., 2017). Moreover, **102** also showed cytotoxicity against KB, MCF-7, and NCI-H187 cell lines, with IC_{50} values of 11.36, 6.45, and 12.81 μg/mL, respectively (Lekphrom et al., 2018).

2.5 Flavone aglycones and isoflavones

To flavone aglycones and isoflavones, 25 structures (Figure 8) were isolated from various Annonaceae species, notably from the genera *Anomianthus*, *Desmos*, *Fissistigma*, *Friesodielsia*, *Melodorum*, *Popowia*, *Uvaria*, and *Cleistochlamys*. These compounds were primarily obtained from leaves, stems, trunks, and roots of plants collected across Southeast Asia and Africa. The identified flavones and isoflavones display considerable structural variation, including *O*-methylation, *O*-prenylation, and substitution with hydroxybenzyl groups, as well as the presence of formyl and methoxy functionalities. Several of these compounds have been reported to exhibit notable biological properties, including cytotoxic, antiplasmodial, anti-inflammatory, antioxidant, and α-glucosidase inhibitory activities. The presence of dihydroxybenzyl-substituted flavones and diverse isoflavone profiles further highlights the chemodiversity and pharmacological potential of flavonoids within this plant family.

The chemical investigation of the leaves of *Anomianthus dulcis* yielded the isolation of chrysin (**103**) (Sinz et al., 1999). Compound **103**, when isolated from other Annonaceae sources, was assayed in different models. When evaluated for its cytotoxicity, it exhibited activity against HepG2 and human acute lymphoblastic leukemia T (MOLT-3) cell lines, with IC_{50} values of 9.7 and 7.2 μg/mL, respectively (Bajgai et al., 2011). In the study by Saadawi et al. (2012), **103** showed strong dose-dependent inhibitory activity on prostaglandin E_2 (PGE_2) production, with an IC_{50} value of 25.5 μM, and also demonstrated inhibitory effects on thromboxane B_2 (TXB_2) production, with an IC_{50} = 39.3 μM. In the study by Hongnak et al. (2015), compound **103** exhibited cytotoxic activity against KB, HeLa, MCF-7, and HepG-2 cell lines, with IC_{50} values (μM) of 26.9, 33.9, 32.5, and 28.9, respectively. The study by Hsu et al. (2016) showed inhibitory effects of **103** on superoxide anion generation and elastase release, with IC_{50} values of 2.25 and 2.44 μM, respectively. The study by Meesakul et al. (2017) exhibited an inhibitory effect of **103** on NO production, with an IC_{50} = 7.56 μM. In other studies, α-glucosidase inhibitory activity was demonstrated for **103** (Meesakul et al., 2019; Do and Sichaem, 2022).

The compound 5,3′-dihydroxy-7-methoxyflavone (**104**) was isolated from the leaves of *Friesodielsia discolor* (Prawat et al., 2012). Compound **104** exhibited cytotoxic activity against the MCF-7 cell line, with an IC_{50} value of 3.45 μg/mL. In the study by Moriyasu et al. (2011), 5,7,8-trimethoxyflavone (**105**) was isolated from the roots of *Uvaria welwitschia* (from Kenya). From the leaves of *Desmos chinensis* collected in Vietnam, negletein (**106**) was isolated and showed inhibitory activity against NFAT transcription, with an IC_{50} = 3.89 μM (Kiem et al.,

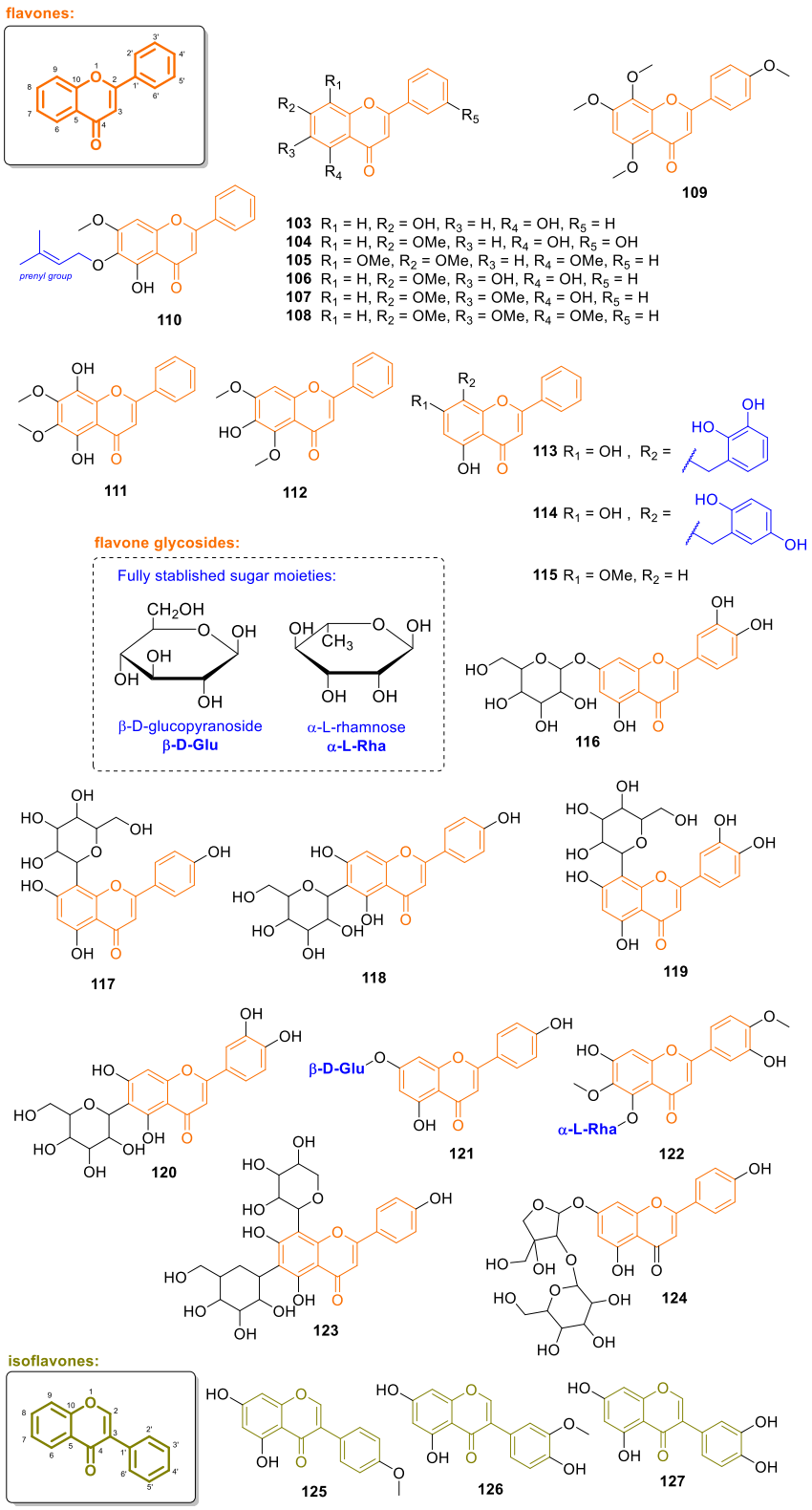

FIGURE 8
Chemical structures of flavones and isoflavones isolated from Annonaceae (**103**–**127**).

2005). Panichpol and Waterman (1978) isolated the compounds 5-hydroxy-6,7-dimethoxyflavone (**107**) and baicalein trimethyl ether (**108**) from the stems of *Popowia cauliflora* (from Cameroon). Compound **107**, also known as isoflavone (Clement et al., 2017), exhibited inhibitory activity on superoxide anion generation with an IC_{50} value of 1.19 μM (Hsu et al., 2016). Moreover, the molecule

tetramethylscutellarein (**109**) was isolated from the leaves of *Cleistochlamys kirkii* (from Tanzania) was reported (Nyandoro et al., 2017).

The chemical investigation of the stem bark of *Melodorum fruticosum* afforded the *O*-prenylated molecule melodorone A (**110**), which showed α-glucosidase inhibitory activity with an IC_{50} of 2.59 μM (Do and Sichaem, 2022). The compound 5,8-dihydroxy-6,7-dimethoxyflavone (**111**) was isolated from the leaves of *Fissistigma lanuginosum* (from Malaysia), displaying a fully substituted ring A (Alias et al., 1995). From the leaves and trunks of *Uvaria flexuosa* the compound 6-hydroxy-5,7-dimethoxyflavone (**112**) was isolated (Hsu et al., 2016). Furthermore, two compounds, named desmoscochinflavones A (**113**) and B (**114**), were isolated from the leaves of *Desmos cochinchinensis* (Meesakul et al., 2019). Compounds **113** and **114** contain a dihydroxybenzyl group on the A-ring, differing only in the position of the hydroxyl groups within this substituent. Moreover, they demonstrated α-glucosidase inhibitory activity, each with an IC_{50} value of 0.9 μM. In the study by Maeda et al. (2020), these compounds were also isolated but referred to with different names. Additionally, tectochrysin (**115**) was isolated from the leaves of *Friesodielsia discolor* (Prawat et al., 2012). Compound **115** exhibited antiplasmodial activity against *Plasmodium falciparum* (IC_{50} = 2.08 μg/mL) and cytotoxic activity against KB (IC_{50} = 14.82 μg/mL) and MCF-7 (IC_{50} = 4.49 μg/mL) cell lines.

From the heartwood of *Anaxagorea luzonensis*, collected in Thailand, Gonda et al. (2000) isolated three isoflavones: biochanin A (**125**), 3′-methylorobol (**126**), and orobol (**127**). In the B-ring, compound **125** contains a methoxy group; compound **126** contains both a methoxy and a hydroxyl group; and compound **127** contains two hydroxyl groups.

2.6 Flavone glycosides

About flavone glycosides, nine structures (Figure 8) were isolated from members of the Annonaceae family, notably from the genera *Artabotrys*, *Alphonsea*, and *Annona*. These compounds were primarily obtained from leaf extracts of species collected in Asia, including China, Thailand, India, and Malaysia. Structurally, these flavonoids include both *C*-glycosylated and *O*-glycosylated derivatives of common aglycones such as apigenin and luteolin. These glycosides demonstrated notable anti-inflammatory activity, as evidenced by their inhibitory effects on the production of PGE_2, cyclooxygenase-2 (COX-2), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) *in vitro*. The occurrence of rare glycosylation patterns, including rhamnosides and apiosyl-glucosides, highlights the structural diversity and potential therapeutic relevance of flavone glycosides in Annonaceae species.

The phytochemical study with the leaves of *Artabotrys hexapetalus* (from China) yielded the compound glucoluteolin (**116**) (Li et al., 1997). Moreover, from the leaves of *Alphonsea elliptica* collected in Malaysia, Attiq et al. (2021) isolated vitexin (**117**), isovitexin (**118**), orientin (**119**), and isoorientin (**120**). These compounds are notable for the presence of a *C*-glycosidic group on the ring A of their structures. These substances exhibited inhibitory activity in PGE_2 and COX-2 assays, with IC_{50} values of 20.5 and 16.6 μM, respectively, for compound **117**; 17.7 and 12.8 μM for **118**; 14.7 and 9.5 μM for **119**; and 11.4 and 7.1 μM for **120**. Furthermore, these compounds showed inhibitory activity in IL-1β and IL-6 assays, with IC_{50} values of 14.5 and 14.0 μM, respectively, for **117**; 10.8 and 11.5 μM for **118**; 6.2 and 5.9 μM for **119**; and 4.8 and 4.0 μM for **120**. In Thailand, Somanawat et al. (2012) isolated the compound apigenin 7-*O*-β-D-glucopyranoside (**121**) from the leaves of *Artabotrys hexapetalus*.

The molecule 5,7,4′-trihydroxy-6,3′-dimethoxyflavone 5-*O*-α-L-rhamnopyranoside (**122**) was isolated from the leaves of *Annona squamosa* (from India) (Panda and Kar, 2015). Additionally, the compound schaftoside (**123**) was isolated from the leaves of *Alphonsea elliptica* (Attiq et al., 2021). Compound **123** exhibited inhibitory activity in the PGE_2 assay, with an IC_{50} value of 77.6 μM. Furthermore, the compound apigenin 7-*O*-apiosyl (1→2) glucoside (**124**) was isolated from the leaves of *Artabotrys hexapetalus* (Li et al., 1997).

2.7 Flavonol aglycones

Regarding flavonol aglycones, 19 distinct structures (Figure 9) have been isolated from various Annonaceae species, particularly from genera such as *Anaxagorea*, *Duguetia*, *Goniothalamus*, *Melodorum*, *Miliusa*, *Alphonsea*, and *Friesodielsia*. These flavonols were primarily obtained from different plant parts, including leaves, stem bark, heartwood, fruits, and aerial parts, collected across Asia, Africa, and South America. This group encompasses widely known natural flavonols, such as quercetin, kaempferol, and myricetin, as well as a range of polymethoxylated or hydroxylated derivatives. Some of these compounds exhibited notable biological activities, including anti-inflammatory, urease-inhibitory, antioxidant, and antiparasitic effects. The widespread occurrence of this subclass in Annonaceae underscores its chemodiversity and therapeutic potential, particularly given the broad spectrum of bioactivities reported for several of these molecules.

The compound aromadendrin (**128**) was isolated from the heartwood of *Anaxagorea luzonensis* (Sabphon et al., 2015). Ngouonpe et al. (2019) isolated the compounds kumatakenin (**129**) and pachypodol (**130**) from the stem barks of *Duguetia staudtii* (from Cameroon). Compounds **129** and **130** exhibited potent urease inhibitory activity, with IC_{50} values of 17.5 and 14.5 μg/mL, respectively, as well as strong anti-inflammatory activity by inhibiting both the myeloperoxidase-dependent (luminol/zymosan) and -independent (lucigenin/PMA) oxidative burst, with potencies expressed as IC_{50} ranging from 4.99 to 14.13 μg/mL (Ngouonpe et al., 2019). Additionally, the compounds 5-hydroxy-3,7-dimethoxy-2-(3-methoxyphenyl)-4*H*-1-benzopyran-4-one (**133**) and 5,4′-dihydroxy-3,7,3′,5′-tetramethoxyflavone (**134**) were also isolated by Ngouonpe et al. (2019). Compound **134** exhibited potent urease inhibitory activity (IC_{50} = 10.9 μg/mL) and strong anti-inflammatory activity by inhibiting both myeloperoxidase-dependent and -independent oxidative burst, with IC_{50} values ranging from 3.89 to 8.55 μg/mL. Furthermore, from the leaves of *Miliusa balansae*, the compound chrysosplenol C (**131**) was described (Thao et al., 2015), while annulatin (**132**) was isolated from the aerial parts of *Goniothalamus gardneri*, (from India) (Seidel et al., 2000).

In the work by Gonda et al. (2000), quercetin (**135**), kaempferol (**136**) and 3,5,7,4′-tetrahydroxy-2′-methoxyflavone (**146**) were

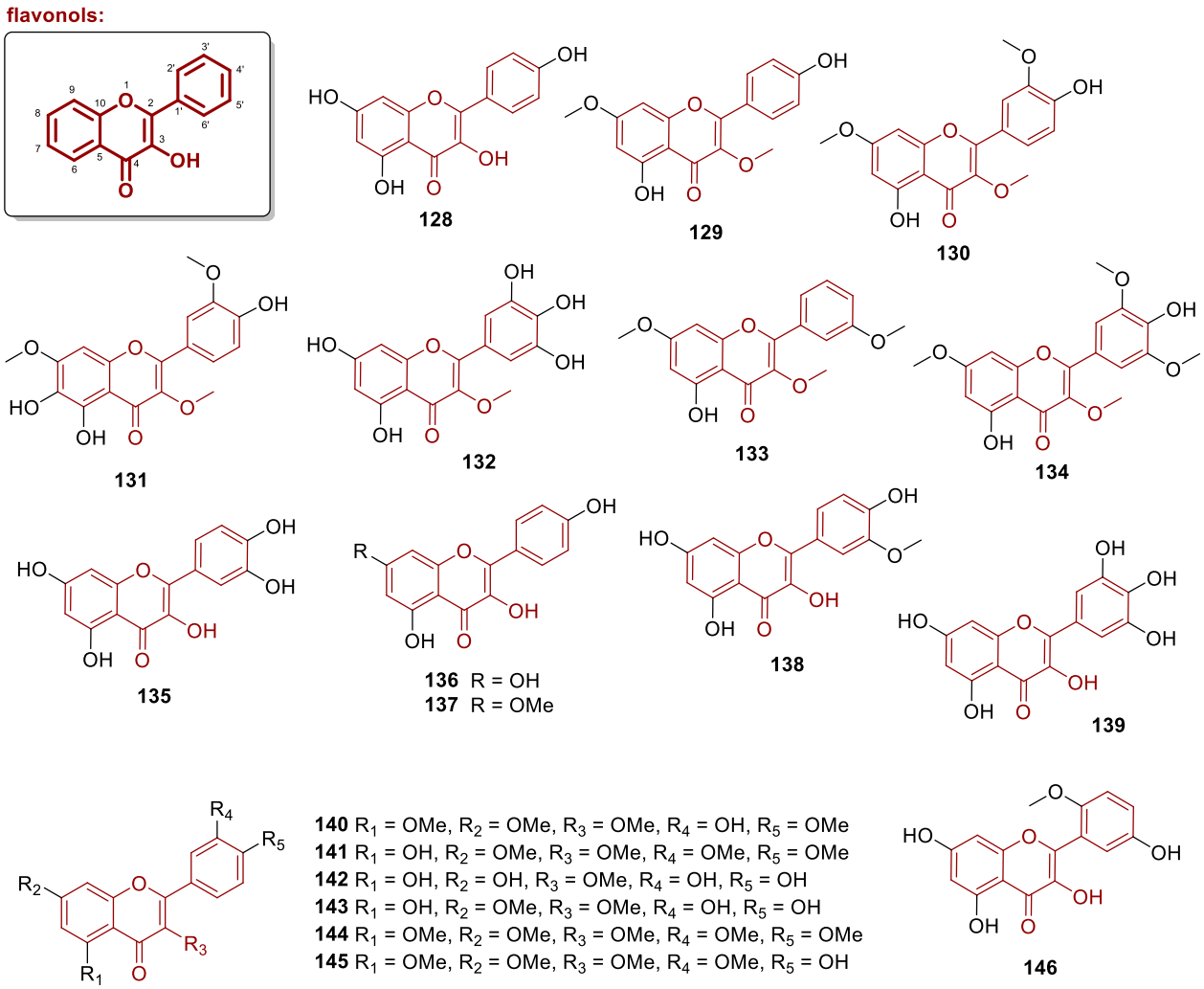

FIGURE 9
Chemical structures of flavonol aglycones isolated from Annonaceae (**128**–**146**).

isolated from the heartwood of *Anaxagorea luzonensis*. These molecules were repeatedly isolated from different Annonaceae sources, and their biological activities were reviewed elsewhere (Wang et al., 2022; Periferakis et al., 2022). The compound kaemferide (**137**) was isolated from the fruits of *Melodorum siamensis* (Jaidee et al., 2019), while isorhamnetin (**138**) was obtained from leaves and twigs of *Duguetia furfuracea* (from Brazil) (Carollo et al., 2006). Compound **138** exhibited antiparasitic activity against *Trypanosoma cruzi*, with an IC_{50} = 4.63 μM. Additionally, the compound myricetin (**139**) was isolated from the leaves of *Alphonsea elliptica* (Attiq et al., 2021). The molecules 3′-hydroxy-3,5,7,4′-tetramethoxyflavone (**140**), 5-hydroxy-3,7,3′,4′-tetramethoxyflavone (**141**), 5,7,3′,4′-tetrahydroxy-3-methoxyflavone (**142**), 5,3′,4′-trihydroxy-3,7-dimethoxyflavone (**143**), 3,5,7,3′,4′-pentamethoxyflavone (**144**), and 4′-hydroxy-3,5,7,3′-tetramethoxyflavone (**145**) were isolated from the leaves of *Goniothalamus tenuifolius* (from Thailand) (Likhitwitayawuid et al., 2006). Among these, only compounds **143** and **144** exhibited antioxidant activity, with IC_{50} values of 6.4 and 5.8 μM, respectively.

2.8 Flavonol glycosides

Flavonol glycosides represent the most diverse flavonoid subclass identified in Annonaceae, comprising at least 59 isolated compounds (Figures 10–13) from a wide range of species, particularly from genera such as *Annona*, *Goniothalamus*, *Uvaria*, *Artabotrys*, *Fissistigma*, *Ellipeiopsis*, *Porcelia*, *Dasymaschalon*, and *Melodorum*. These glycosides are predominantly *O*-glycosylated at the C-3 position of the aglycone and feature mono-, di-, or trisaccharide moieties composed of glucose, galactose, rhamnose, arabinose, xylose, or apiose, often in branched configurations. Several derivatives also contain acyl substituents, such as *p*-coumaroyl, feruloyl, or sinapoyl groups. The structural complexity is reflected in a wide array of biological properties, including antioxidant, cytotoxic, anti-inflammatory, and larvicidal activities. This high structural variability and consistent biological potential underscore the phytochemical richness and pharmacological relevance of flavonol glycosides within the family.

This group of substances is widespread among Annonaceae with several examples, such as the isolation of mearnsitrin (**147**), which

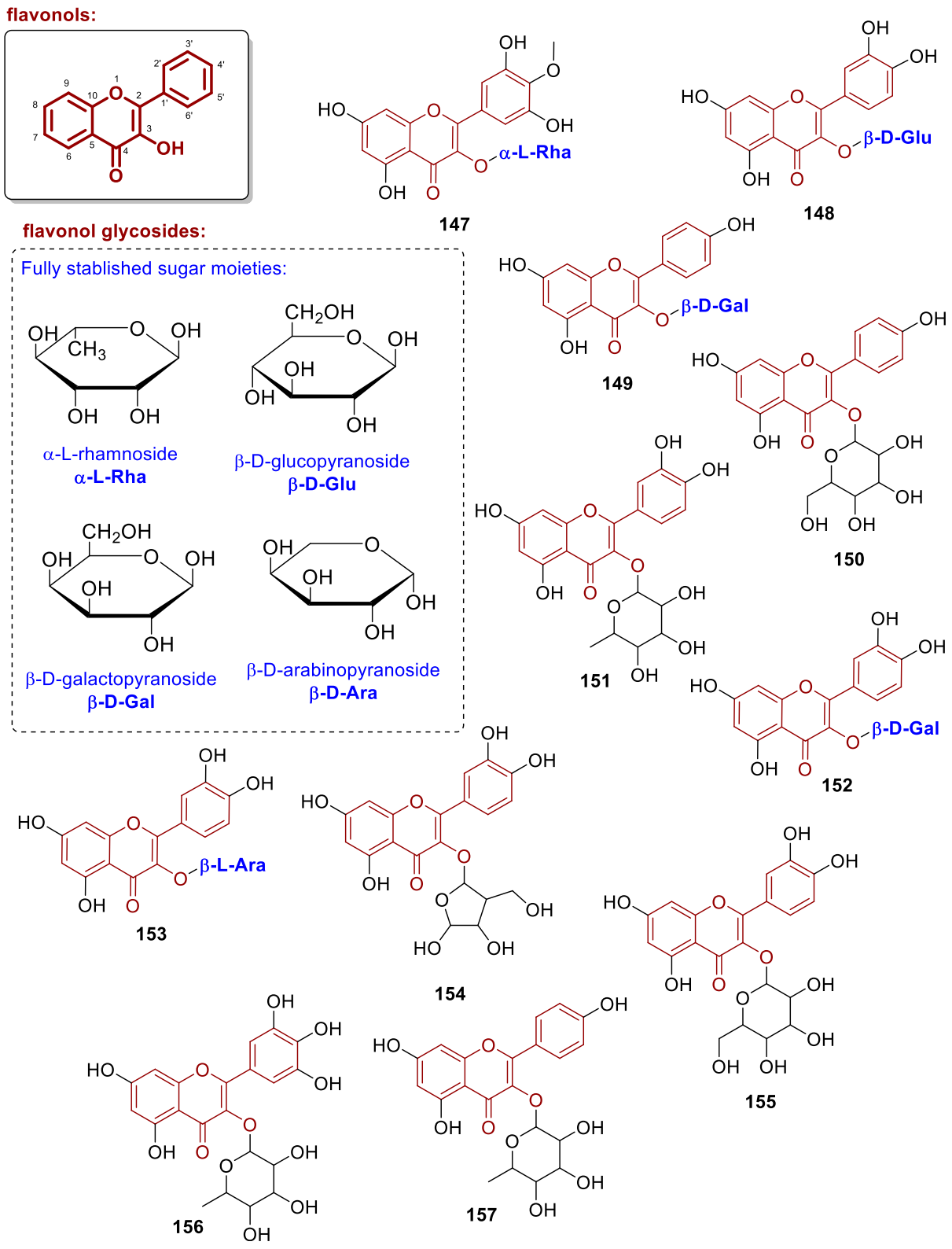

FIGURE 10
Chemical structures of flavonol glycosides isolated from Annonaceae (**147**–**157**).

contains an *O*-α-L-rhamnopyranose at C-3 from the aerial parts of *Goniothalamus gardneri* (Seidel et al., 2000). The compound isoquercitrin (**148**) was first isolated in Annonaceae from the leaves of *Uvaria rufa* (Deepralard et al., 2009). Later, it was re-isolated and pharmacologically evaluated by Ngoc et al. (2019), showing prevention of intracellular ROS formation in BEAS-2B cells

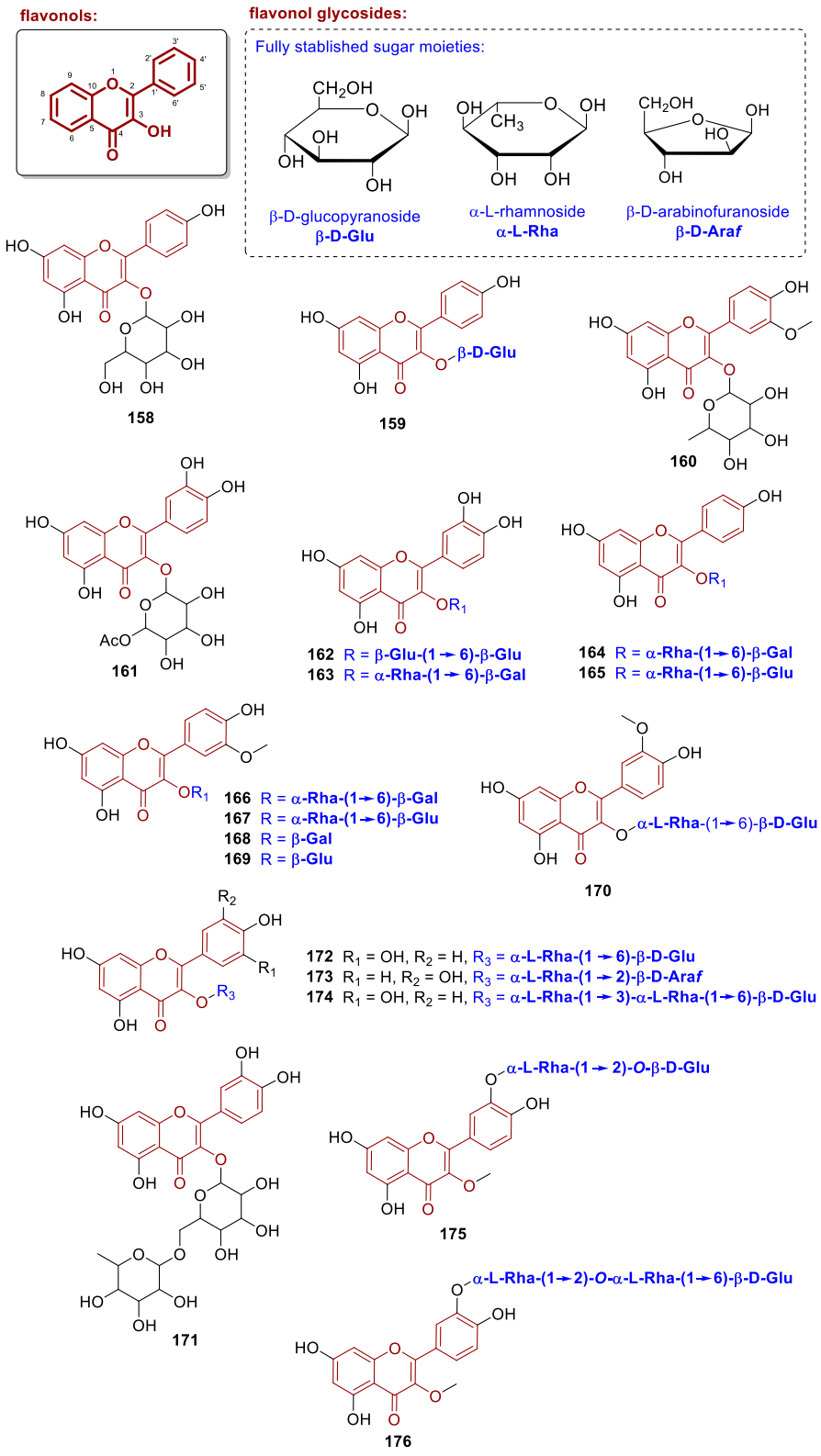

FIGURE 11
Chemical structures of flavonol glycosides isolated from Annonaceae (**158**–**176**).

treated with AAPH, with an IC_{50} = 24.1 μM. Moreover, in the work of Zhu et al. (2020), this compound exhibited antioxidant activity, with an IC_{50} value of 69.13 μg/mL. Furthermore, the compounds kaempferol 3-*O*-β-D-galactopyranoside (**149**) (leaves of *Annona dioica*, Paraguay) (Vega et al., 2007) and 3-*O*-β-glucoside (**150**) (leaves of *Annona classiflora*, Brazil) (Rocha et al., 2016) were

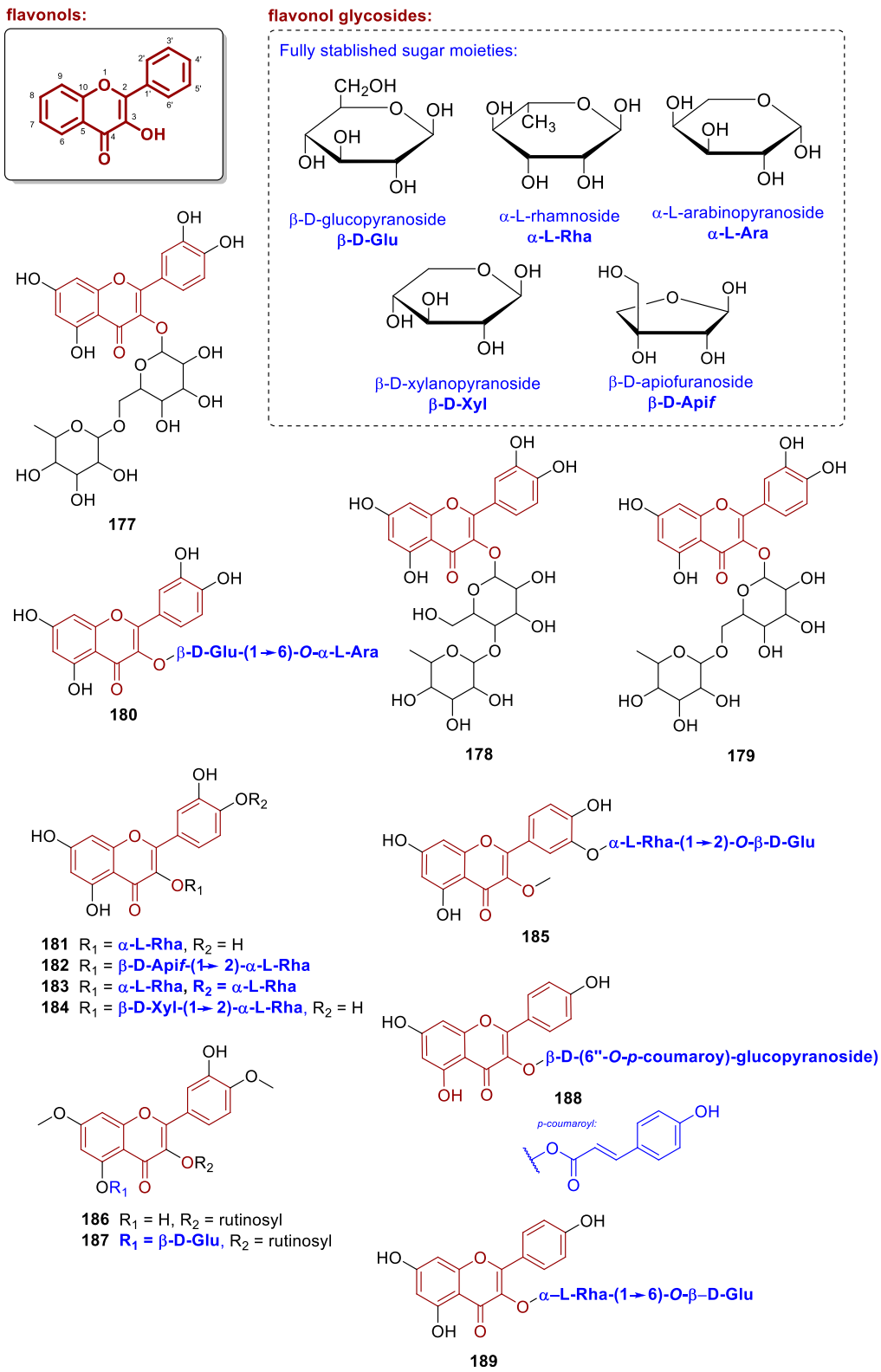

FIGURE 12
Chemical structures of flavonol glycosides isolated from Annonaceae (**177**–**189**).

isolated, and solely **149** had the glycosyl moiety fully established. Additionally, quercetin-3-*O*-rhamnoside (**151**) was isolated from the leaves of *Annona purpurea* (From Taiwan) (Chang et al., 1998).

From the leaves of *Annona crassiflora* (from Brazil), the compounds quercetin-3-*O*-β-D-galactopyranoside (**152**) and quercetin-3-*O*-β-L-arabinopyranoside (**153**), which exhibited

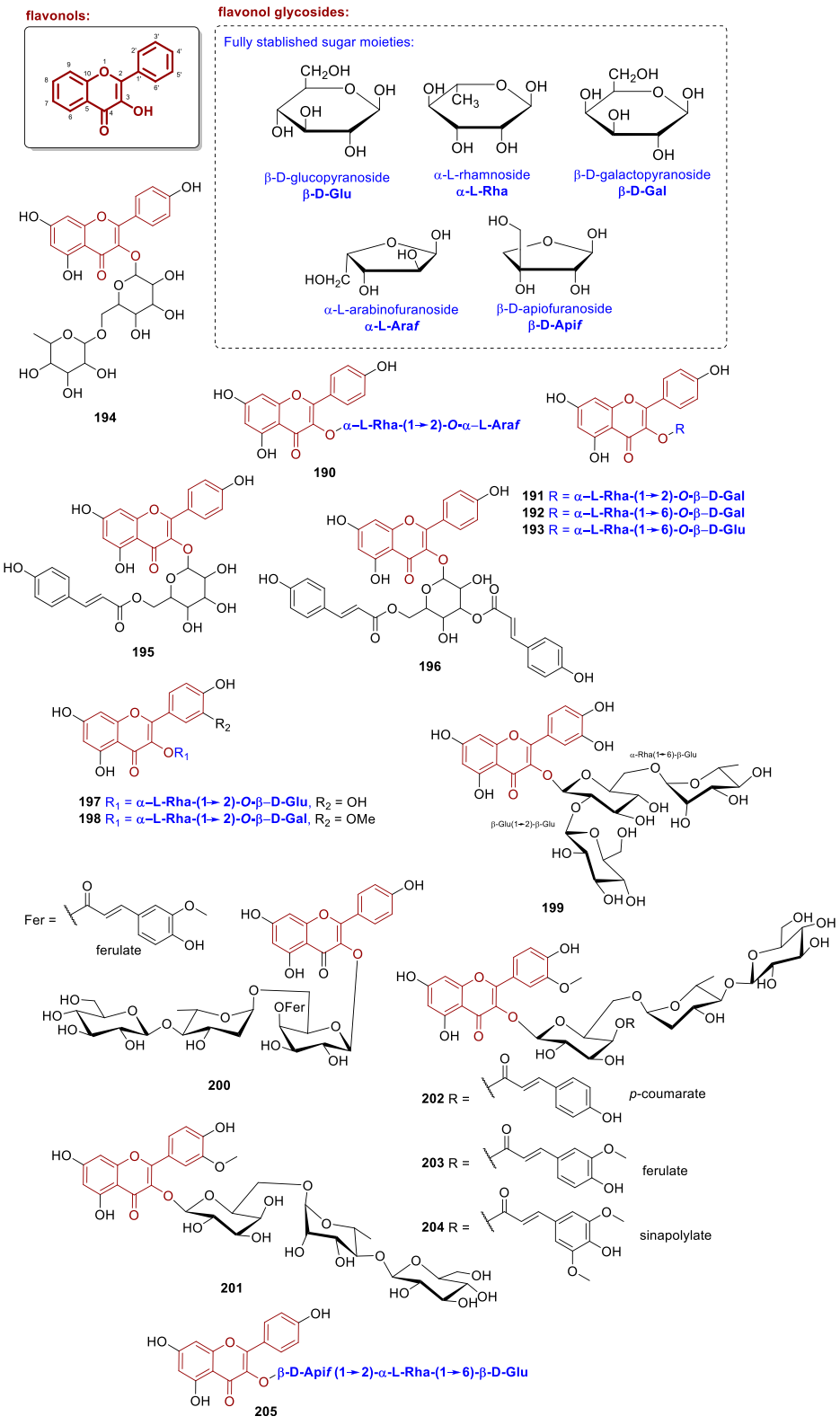

FIGURE 13
Chemical structures of flavonol glycosides isolated from Annonaceae (**190**–**205**).

larvicidal activity with LD_{50} values of 103.74 and 109.52 μg/mL, respectively (Lage et al., 2014). Additionally, quercetin-3-*O*-arabinofuranoside (**154**) from the leaves of *Xylopia emarginata* (from Brazil) (Moreira et al., 2003), quercetin-3-*O*-β-galactoside (**155**) and kaempferol-3-*O*-β-galactoside (**158**) from the leaves of *Annona dioica* (from Brazil) (Formagio et al., 2013), tanarixetin-3-

O-rhamnoside (**156**) and kaempferol-3-*O*-rhamnoside (**157**) from *Annona purpurea* (from Taiwan) (Chang et al., 1998) were isolated, but the absolute stereochemistry of the glycosyls not established.

Astragalin (**159**), displaying a 3-*O*-β-D-glucopyranoside, was isolated from the leaves of *Uvaria rufa* (Deepralard et al., 2009). Compound **159**, when evaluated by Araujo-Padilla et al. (2022), displayed cytotoxic activity against human immortalized keratinocyte cell line (HaCaT), HeLa, HepG2, and human triple-negative breast cancer cell line (MDA-MB-231) cell lines, with IC_{50} values of 170.2, 92.85, 81.70, and 84.28 μg/mL, respectively. Besides, the compounds isorhamnetin-3-*O*-rhamnoside (**160**) from the leaves of *Annona purpurea* (Chang et al., 1998), isoquercitrin-6-acetate (**161**) from the leaves of *Uvaria rufa* (Deepralard et al., 2009) were isolated.

The compounds quercetin-3-*O*-gentiobioside (**162**), quercetin-3-*O*-robinobioside (**163**), biorobin (**164**), nicotiflorin (**165**), keioside (**166**), narcissin (**167**), cacticin (**168**), and isorhamnetin-3-*O*-β-D-glucoside (**169**) were isolated from the leaves of *Annona coriacea* (from Brazil) (Novaes et al., 2018). Compound **162** features two glucose units connected via a β1→6 glycosidic bond, whereas **163** has a galactose at C-3 linked to a rhamnose at C-6″ (β1→6α). Compounds **164** and **165** follow the same pattern but with kaempferol as the aglycone. Compounds **166** and **167** also share this linkage pattern, with isorhamnetin as the aglycone. Finally, **168** and **169** are monoglycosides containing galactose and glucose, respectively, directly linked at the C-3 position of isorhamnetin (Novaes et al., 2018).

From the leaves of *Fissistigma acuminatissima*, Van et al. (2007) isolated isorhamnetin-3-*O*-rutinoside (**170**), a diglycosylated flavonoid whose structure contains a glucose unit in pyranoside form, with β-anomeric and D-absolute configurations, *O*-glycosidically linked to the hydroxyl group at the C-3 position of the aglycone. Furthermore, this glucose is branched at position 6″ by a rhamnose unit in pyranoside form through an (α1→6β) linkage. Moreover, quercetin-3-*O*-β-glucoside-6-*O*-α-rhamnoside (**171**) was isolated from the pulp of *Annona cacans* (from Brazil) (Volobuff et al., 2019).

Somanawat et al. (2012), studied the leaves of *Artabotrys hexapetalus* (from Thailand) and isolated the compound quercetin 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**172**) and 3-*O*-α-L-rhamnopyranosyl-(1→3)-*O*-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside] (**174**). Compound **174** is a triglycosylated flavonoid with a glucose unit in pyranoside form, bearing β-anomeric and D-absolute configuration, *O*-glycosidically linked to the hydroxyl group at the C-3 position of quercetin. The glucose is branched at positions 6″ and 3″ by two rhamnose units in pyranoside form, both with α-anomeric and L-absolute configuration, via (α1→6α) and (α1→3β) linkages, respectively. Moreover, the compound arapetaloside A (**173**) was isolated from the leaves of *Artabotrys hexapetalus* (from China) by Li et al. (1997). This compound contains an arabinose unit in furanoside form, with α-anomeric and L-absolute configuration, *O*-glycosidically linked to the C-3 position of quercetin. In addition, this arabinose is branched at position 2″ by a rhamnose unit in pyranoside form, linked via an (α1→2β) bond.

The compounds quercetin-3,7-dimethyl ether 3′-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-galactopyranoside (**175**) and quercetin-3,7-dimethyl ether 3′-*O*-α-L-rhamnopyranosyl-(1→2)-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**176**) were isolated from the leaves of *Dasymaschalon sootepense* (from Thailand) (Sinz et al., 1998). These compounds differ by the presence of an additional rhamnose unit at the 6″ position of the glucose moiety in compound **176**, whereas compound **175** contains only the rhamnose at position 2″ of the galactose unit.

Furthermore, other analogues were isolated from different Annonaceae sources, such as 3-*O*-robinoside (**177**) and quercetin 3-*O*-neohesperidoside (**178**) from the leaves of *Annona muricata* (from Egypt) (Nawwar et al., 2012), quercetin 3-*O*-rutinoside (rutin, **179**) from the leaves of *Uvaria rufa* (Deepralard et al., 2009), quercetin-3-*O*-β-D-glucopyranosyl-(1→6)-*O*-α-L-arabinoside (**180**) from the leaves of *Annona crassiflora* (Lage et al., 2014) and quercetin 3-*O*-α-L-rhamnopyranoside (**181**) from the leaves of *Xylopia emarginata* (from Brazil) (Moreira et al., 2003). Compound **181** was re-isolated by Ngoc et al. (2019) and had its potential to prevent intracellular ROS formation in BEAS-2B cells treated with AAPH evaluated, reporting an IC_{50} of 18.8 μM.

The compounds quercetin 3-*O*-β-D-apiofuranosyl-(1→2)-α-L-rhamnopyranoside (**182**), quercetin 3,3′-*O*-di-α-L-rhamnopyranoside (**183**), quercetin 3-*O*-β-D-xylopyranosyl-(1→2)-α-L-rhamnopyranoside (**184**), and quercetin 3-methoxy-3′-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside (**185**) were isolated from the stems of *Fissistigma polyanthoides* (from Vietnam) (Ngoc et al., 2019). Compounds **182**–**184** were evaluated for their antioxidant activity in BEAS-2B cells, with the following IC_{50} values for inhibition of intracellular ROS formation: 38.5 μM (**182**), 18.8 μM (**183**), 35.3 μM (**184**).

From the branches of *Porcelia macrocarpa* collected in Brazil, Chaves et al. (2004) isolated the glycosylated flavonoids quercetin-3-*O*-rutinoside-7,4′-dimethyl ether (**186**) and quercetin-5-*O*-glycoside-3-*O*-rutinoside-7,4′-dimethyl ether (**187**). Compound **186** contains two sugar units (rutinosides) and two methoxyl groups at positions 7 and 4′ of the flavonoid core, with a free hydroxyl group at C-5. In comparison, compound **187** contains three sugar units (rutinoside and glucoside), however the absolute stereochemistry was not determined. On the other hand, Wirasathien et al. (2006) isolated the compound tiliroside (**188**) from the aerial parts of *Ellipeiopsis cherrevensis* (from Thailand). Compound **188** consists of a kaempferol core glycosylated at position C-3 with a β-D-glucopyranose unit, which is acylated at position 6″ with a *p*-coumaroyl group. Furthermore, the leaves of *Annona squamosa*, collected in China, were studied by Zhu et al. (2020), from which the compound kaempferol-3-*O*-robinobioside (**189**) was isolated. Additionally, antioxidant activity was reported, with an IC_{50} value of 191.67 μg/mL in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay. Compound **189** consists of a kaempferol unit linked at position C-3 to a robinobiose moiety, established as L-Rha(α1→6 β)D-Glu.

From the leaves of *Artabotrys hexapetalus*, the compound arapetaloside B (**190**) was isolated and determined to contain two sugar units, forming a diglycoside in which a rhamnose is linked to an arabinose, which is in turn attached to kaempferol at the C-3 position (Li et al., 1997). Moreover, from the leaves of *Fissistigma pallens*, collected in Vietnam, three glycosylated flavonoids: kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-galactopyranoside (**191**), kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-galactopyranoside (**192**), and kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside

(**193**) were isolated (Nhiem et al., 2019). These compounds were evaluated for cytotoxic potential against human colorectal adenocarcinoma (HT-29), human malignant melanoma (A-2058), and human lung adenocarcinoma (A-549) cell lines. Compound **191** showed IC_{50} values of 141.9 μM, 144.9 μM, and 136.2 μM, respectively. Compound **192**, the observed values were 150.5 μM, 143.6 μM, and 149.0 μM. Compound **193** exhibited IC_{50} values of 147.4 μM, 143.3 μM, and 145.7 μM against the same cell lines, respectively. Additionally, from the aerial parts of *Ellipeiopsis cherrevensis*, the compound kaempferol 3-*O*-rutinoside (**194**) was isolated (Wirasathien et al., 2006).

Vega et al. (2007) isolated the flavonoids 6″-*O*-*p*-hydroxycinnamoyl-β-galactopyranosyl-kaempferol (**195**) and 3-*O*-[3″,6″-di-*O*-*p*-hydroxycinnamoyl]-β-galactopyranosyl-kaempferol (**196**) from the leaves of *Annona dioica*. Both compounds were evaluated for cytotoxic activity against Ehrlich carcinoma cells, exhibiting IC_{50} values of 14.7 μM for compound **195** and 10.9 μM for compound **196**. Moreover, the flavonoids rhamnetin 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside (**197**) and isorhamnetin 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-galactopyranoside (**198**) were isolated from the leaves of *Fissistigma pallens* (Nhiem et al., 2019). Both compounds were evaluated for cytotoxic activity against HT-29, A-2058, and A-549 cell lines, showing IC_{50} values of 137.9, 156.6, and 144.2 μM for compound **197** and 150.0, 153.8, and 141.3 μM for compound **198**, respectively. Moreover, the same study described the flavonoids fissflavoside A (**202**), fissflavoside B (**203**), and fissflavoside C (**204**). These compounds are acylated kaempferol triglycosides, with a trisaccharide linked at position 3 of the aglycone, composed of β-D-galactopyranose (acylated at position 4), L-Rha(α1→6), and D-Glu(β1→4). The difference among the three compounds lies in the acyl group present on the galactose unit: p-coumaroyl in **202**, feruloyl in **203** and sinapoyl in **204**. All three flavonoids were evaluated for their cytotoxic activity against HT-29, A-2058, and A-549 cell lines, with IC_{50} values of 150.5, 162.6, and 161.7 μM for **202**, 161.6, 149.1, and 160.4 μM for **203** and 158.7, 158.7, and 155.7 μM for **204**, respectively (Nhiem et al., 2019).

Furthermore, the compound quercetin 3-*O*-α-rhamnosyl-(1″→6″)-β-sophoroside (**199**) was isolated from the leaves of *Annona muricata* (Nawwar et al., 2012). The chemical investigation of the leaves of *Fissistigma maclurei* collected in Vietnam, yielded the isolation of the compounds kaempferol 3-*O*-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→6)-[4-(*E*)-feruloyl]-β-D-galactopyranoside (**200**) and fissmacoside A (**201**) (Ba et al., 2020). Compound **202** is a triglycosylated flavonol consisting of an isorhamnetin moiety linked at position C-3 to a trisaccharide composed of D-Glu(β1→4α)L-Rha(α1→6β)D-Gal. Finally, the leaves of *Melodorum fruticosum* were studied by Chan et al. (2013), who isolated the flavonoid kaempferol 3-*O*-β-D-apiofuranosyl-(1→2)-*O*-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside (**205**).

2.9 Dihydroflavonols

Dihydroflavonols are less frequently reported in Annonaceae but include notable representatives characterized by 2,3-dihydro-2-phenylchromen-4-one cores with hydroxylation patterns similar to their flavonol counterparts. A total of five compounds (Figure 14) have been identified, primarily featuring glycosylation at the C-3 position, with sugar residues such as glucose, galactose, quinovose, and rhamnose. The absolute stereochemistry, predominantly (2R, 3R), was confirmed for several compounds through circular dichroism analysis or comparison with authentic standards. While structurally simpler than other subclasses, dihydroflavonols have demonstrated antioxidant and moderate enzyme-inhibitory activities, as evidenced by their ability to inhibit ROS. These findings indicate that, despite their lower diversity, dihydroflavonols represent a biologically relevant but underexplored class within the Annonaceae.

The compounds (2*R*,3*R*)-taxifolin-3-*O*-β-D-quinovopyranoside (**206**), (2*R*,3*R*)-taxifolin-3-*O*-β-D-glucopyranoside (**207**), and (2*R*,3*R*)-taxifolin-3-*O*-β-D-galactopyranoside (**208**) were isolated from the stems of *Fissistigma polyanthoides* (Ngoc et al., 2019). The absolute configuration of the isolated compounds was determined by circular dichroism. Compounds **206** and **207** demonstrated the ability to inhibit the intracellular formation of reactive oxygen species (ROS) in BEAS-2B cells, with IC_{50} values of 61.4 μM and 63.5 μM, respectively. Moreover, from the leaves of *Desmos chinensis*, collected in Vietnam, the compound astilbin (**209**), a dihydroflavonol 3-*O*-α-L-rhamnoside, was isolated, as reported by Kiem et al. (2005). Its absolute configuration was determined as (2*R*,3*R*) by comparison with literature data. In the NFAT-mediated transcription inhibition assay, **209** did not show an IC_{50} lower than 50 μM. Besides, from the leaves of *Artabotrys hexapetalus*, collected in China, taxifolin (**210**) was isolated (Li et al., 1997). Compound **210** exhibited inhibitory activity against phosphodiesterase type 5 (PDE5), with inhibition rates of 14.0% and 7.8% at concentrations of 100 μM and 10 μM, respectively (Sabphon et al., 2015).

2.10 Catechins

A total of three catechin-related compounds (Figure 14) have been isolated primarily from the leaves and stems of species belonging to the genera *Annona* and *Fissistigma*. The compound (−)-*epi*catechin (**211**) was isolated from the leaves of *Annona classiflora*, (Lage et al., 2014). Its antimicrobial activity was evaluated, showing a growth inhibition (GI) of 86% against *Staphylococcus aureus* and 5.5% against *Escherichia coli*. In the study by Ngoc et al. (2019), this compound exhibited an IC_{50} of 47.0 μM in the prevention of intracellular reactive oxygen species (ROS) formation in BEAS-2B cells treated with AAPH. Moreover, the chemical study of the leaves of *Fissistigma acuminatissima* (from Vietnam) was isolated (+)-catechin (**212**). Ngoc et al. (2019) studied the stems of *Fissistigma polyanthoides* and isolated catechin-3-*O*-α-L-rhamnopyranoside (**213**). This compound showed an IC_{50} value of 47.9 μM in the prevention of intracellular ROS formation in BEAS-2B cells treated with AAPH.

2.11 Miscellaneous compounds

A diverse array of 25 structurally complex flavonoid-related compounds (Figure 15), classified as miscellaneous derivatives, has been isolated from various Annonaceae species. These compounds

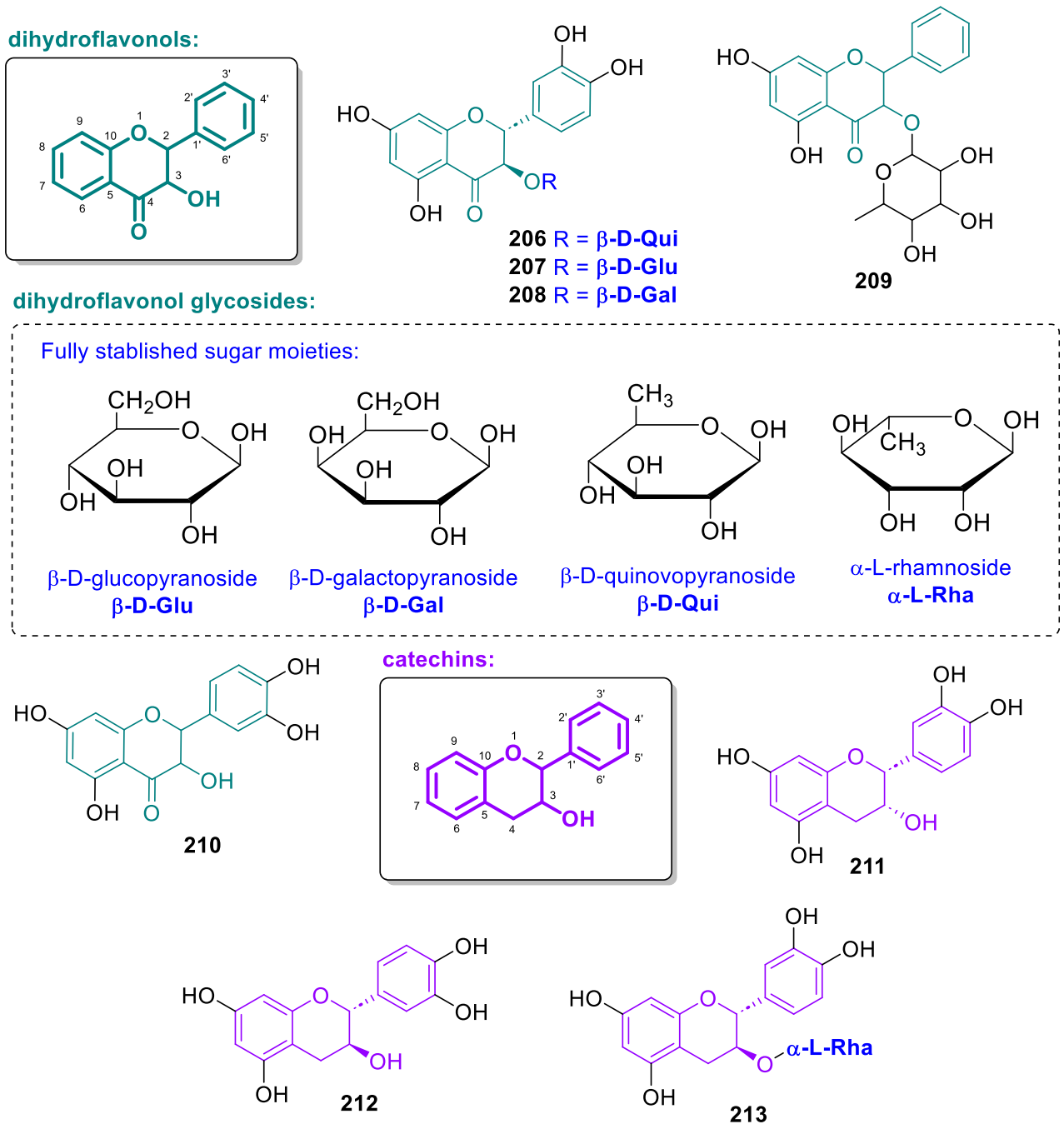

FIGURE 14
Chemical structures of dihydroflavonols and catechins isolated from Annonaceae (**206**–**213**).

include rare biflavonoids, sesquiterpene-flavonoid hybrids, flavan–flavanone dimers, and acylated flavonoids, among others. The majority were obtained from the leaves and branches, with a few isolated from roots and aerial parts. Genera such as *Fissistigma*, *Desmos*, *Friesodielsia*, *Goniothalamus*, and *Uvaria* were the primary sources of these unusual metabolites.

The phytochemical study of the leaves and branches of *Fissistigma bracteolatum* collected in Vietnam, afforded four compounds: fissistigmatins A (**214**), B (**215**), C (**216**), and D (**217**) (Porzel et al., 2000). Compounds **214**–**217** are hybrids of flavonoids with sesquiterpenes. The absolute configuration was determined by X-ray crystallography and molecular modeling studies, with congeners A, C, and D assigned as (4*R*), and fissistigmatin B as (4*S*). Furthermore, from the leaves of *Desmos cochinchinensis* (from Thailand) were isolated the compounds desmosflavan A (**218**) and B (**219**), characterized as flavan-chalcones dimers (Bajgai et al., 2011). Their absolute configurations were determined by circular dichroism as (2*S*,4*S*) for compound **218** and (2*S*,4*R*) for compound **219**. In the same study, compound **218** exhibited lipoxygenase inhibitory activity

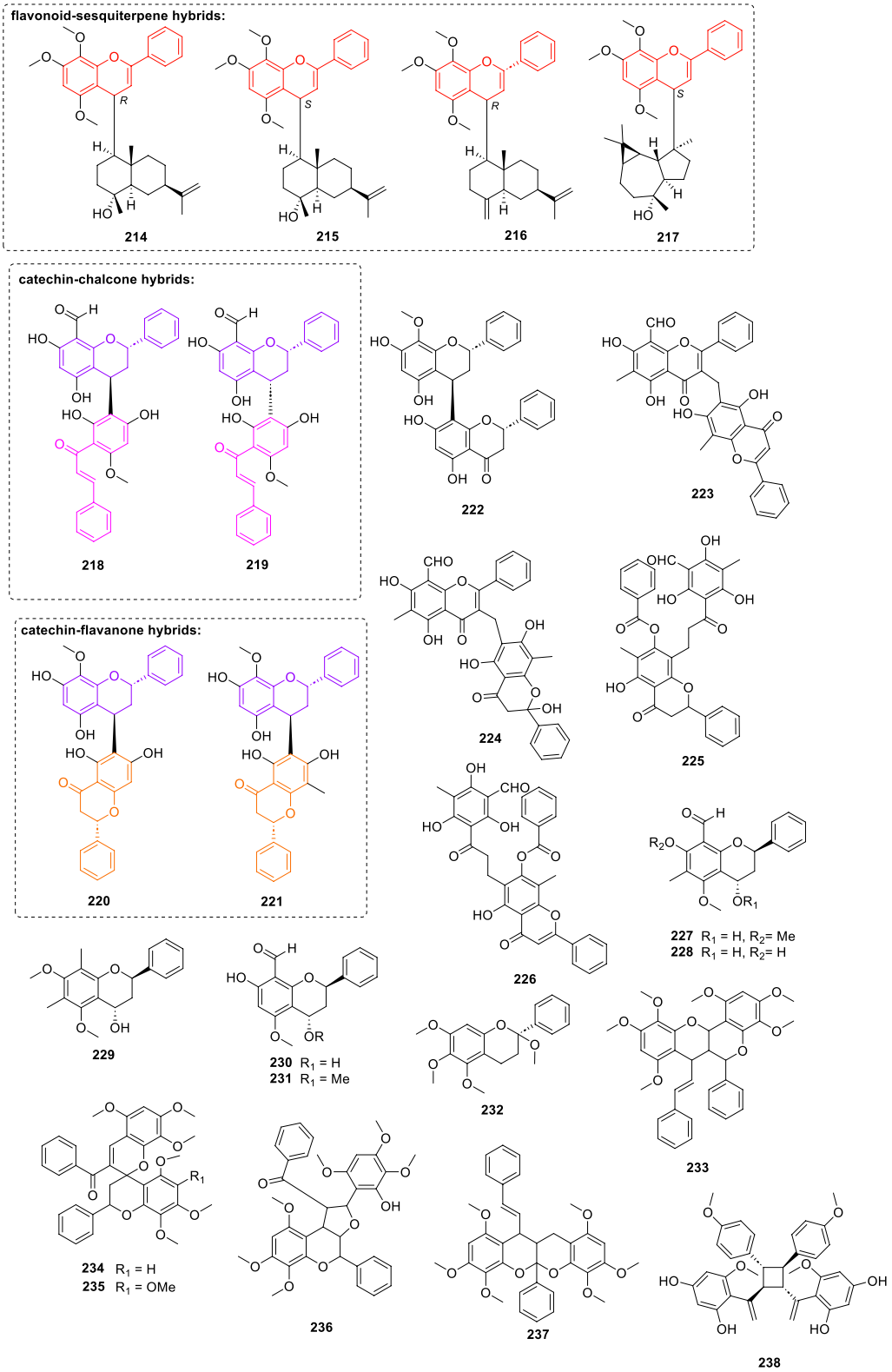

FIGURE 15
Chemical structures of miscellaneous compounds isolated from Annonaceae (**214**–**238**).

with an IC_{50} of 4.4 μM, whereas compound **219** was inactive. In cytotoxicity assays, compound **218** showed activity against HuCCA-1 (2.25 μg/mL), HepG2 (3.75 μg/mL), A549 (2.45 μg/mL), and MOLT-3 (0.29 μg/mL), while compound **219** exhibited IC_{50} values of 22.0 μg/mL, 20.3 μg/mL, 27.0 μg/mL, and 1.71 μg/mL against the same cell lines, respectively (Bajgai et al., 2011).

The compounds friesodielsones A (**220**), B (**221**), and C (**222**), classified as flavan–flavanones dimers, were isolated from the leaves and branches of *Friesodielsia desmoides* (Meesakul et al., 2017). Their absolute configurations were determined as 2*S*,4*S* based on circular dichroism analysis. Compound **220** exhibited an IC_{50} of 10.21 μM in nitric oxide inhibition assays in J774.A1 macrophages. Moreover, Rittiwong et al. (2011), in their study of the leaves of *Desmos chinensis* collected in Thailand, isolated saiyutones A (**223**), B (**224**), C (**225**), and D (**226**), unusual biflavonoids. Compounds **223** and **224** possess a unique biflavonoid skeleton with a 3–6″ linkage through a methylene group, while the formation of a cyclic hemiacetal was proposed as a key step in the biosynthetic pathway of saiyutones **225** and **226**.

The flavan derivatives 5,7-dimethoxy-8-formyl-4-hydroxy-6-methylflavan (**227**), 5-methoxy-8-formyl-4,7-dihydroxy-6-methylflavan (**228**), 5,7-dimethoxy-4-hydroxy-6,8-dimethylflavan (**229**), 5-methoxy-8-formyl-4,7-dihydroxyflavan (**230**) and 4,5-dimethoxy-8-formyl-7-hydroxyflavan (**231**) were isolated from the roots of *Desmos cochinchinensis* (Prachyawarakorn et al., 2013). Compounds **227**–**231**exhibited aromatase inhibitory activity with IC_{50} values of 80.0 nM, 1,010 nM, 10,700 nM, 40.0 nM, and 90.0 nM, respectively. Furthermore, Lan et al. (2012), in their study of *Fissistigma latifolium*, isolated 2,5,6,7-tetramethoxyflavan (**232**), which showed superoxide anion inhibition activity in fMLP (N-formylmethionyl-leucyl-phenylalanine)/cytochalasin B-activated human neutrophils, with an IC_{50} of 6.0 μM.

From the roots of *Uvaria welwitschii* collected in Kenya were isolated the compounds dependensin (**233**), welwitschin E (**234**), welwitschin F (**235**), welwitschin G (**236**), and welwitschin H (**237**) (Moriyasu et al., 2011). Additionally, from the aerial parts of *Goniothalamus gardneri* was isolated (*rel*)-1β,2α-di-(2,4-dihydroxy-6-methoxybenzoyl)-3β,4α-di-(4-methoxyphenyl)-cyclobutane (**238**), a symmetric dimer derived from dihydroxychalcones (Seidel et al., 2000). This compound features a symmetrical chalcone dimer structure, containing a cyclobutane ring substituted with two identical A/A′ rings bearing 2,4-dihydroxy-6-methoxy groups and two identical B/B′ rings with 4-methoxyphenyl groups. The presence of a symmetry plane and the arrangement of the aromatic rings in opposite positions allowed the assignment of the relative stereochemistry as (*rel*)-1β,2α,3β,4α.

A comprehensive summary of all identified flavonoid compounds and their reported biological activities is presented in Supplementary Table S1 at the end of this article.

3 Concluding remarks

This review highlights the remarkable, yet underexplored, flavonoid diversity within the Annonaceae family. Our analysis confirms that flavonol glycosides are the most frequently reported class of flavonoids, closely followed by flavanones. Other structural types such as chalcones, dehydrochalcones, isoflavanones, flavonol aglycones, dehydroflavonols, catechins, and miscellaneous compounds were also identified, underscoring a broad chemical spectrum within the family. Notably, prior reports have identified glycosides of both flavones (e.g., apigenin, luteolin) and flavonols (e.g., kaempferol, quercetin, isorhamnetin), with a clear predominance of flavonol derivatives across multiple species. Geographically, Asia emerges as the most significant contributor to the current knowledge base, with Thailand and Vietnam standing out due to the high frequency of studies. Additional contributions from Malaysia, India, Bangladesh, Taiwan, and China reinforce Asia's significant role in the phytochemical investigation of Annonaceae. Africa also plays a prominent part, especially through work conducted in Tanzania, Ghana, Nigeria, Kenya, and Cameroon. In the Americas, Brazil leads the regional representation, followed distantly by Mexico and Paraguay. Notably, no relevant reports were identified from Europe, Oceania, or Antarctica, reflecting potential gaps in geographic sampling or research prioritization. The most cited genus across studies was *Uvaria*, with numerous species such as *U. lucida*, *U. chamae*, *U. ferruginea*, and *U. angolensis* frequently appearing in the literature. *Melodorum* was also highly represented, especially *M. fruticosum*, followed by genera such as *Fissistigma*, *Annona*, *Desmos*, *Friesodielsia*, *Goniothalamus*, *Xylopia*, and *Anaxagorea*. These genera demonstrate not only high species richness but also strong research interest due to their phytochemical potential. The analysis of plant material sources revealed a marked preference for leaf extracts, which are by far the most commonly used in flavonoid studies within Annonaceae. This is followed by extracts from roots and stem bark, while branches and fruits have been investigated less frequently. In summary, while significant strides have been made in identifying flavonoids within Annonaceae, this review underscores a critical need for more systematic and integrative research. A clearer understanding of flavonoid distribution, biosynthesis, and biological roles across the family could illuminate new avenues in pharmacology, taxonomy, and plant ecology.

Author contributions

IG: Writing – review and editing, Writing – original draft, Methodology, Data curation. MB: Writing – review and editing, Data curation, Methodology, Writing – original draft. MP: Writing – review and editing. FD: Data curation, Validation, Software, Project administration, Formal Analysis, Methodology, Visualization, Funding acquisition, Conceptualization, Writing – review and editing, Investigation, Supervision, Resources, Writing – original draft. HK: Project administration, Writing – original draft, Supervision, Data curation, Visualization, Methodology, Formal Analysis, Validation, Conceptualization, Software, Investigation, Funding acquisition, Resources, Writing – review and editing.

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