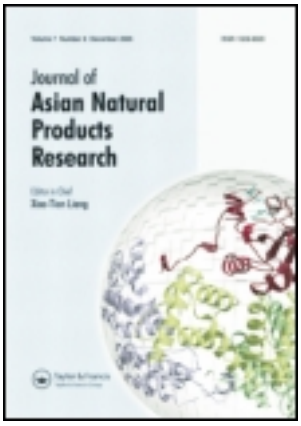

Journal of Asian Natural Products Research

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ganp20

Annonaceae: bio-resource for tomorrow's drug discovery

Noushin Aminimoghadamfarouj [a], Alireza Nematollahi [a] & Christophe Wiart [b]

[a] School of Pharmacy, Faculty of Science, University of Nottingham, Nottingham, 43500, Malaysia

[b] School of Biomedical Sciences, Faculty of Science, University of Nottingham, Nottingham, 43500, Malaysia

Available online: 29 Apr 2011

To cite this article: Noushin Aminimoghadamfarouj, Alireza Nematollahi & Christophe Wiart (2011): Annonaceae: bio-resource for tomorrow's drug discovery, Journal of Asian Natural Products Research, 13:05, 465-476

To link to this article: http://dx.doi.org/10.1080/10286020.2011.570265

Journal of Asian Natural Products Research
Vol. 13, No. 5, May 2011, 465–476

Annonaceae: bio-resource for tomorrow's drug discovery

Noushin Aminimoghadamfarouj[a]*, Alireza Nematollahi[a] and Christophe Wiart[b]

[a]*School of Pharmacy, Faculty of Science, University of Nottingham, Nottingham 43500, Malaysia;* [b]*School of Biomedical Sciences, Faculty of Science, University of Nottingham, Nottingham 43500, Malaysia*

(*Received 13 December 2010; final version received 7 March 2011*)

One of the rich sources of lead compounds is the Angiosperms. Many of these lead compounds are useful medicines naturally, whereas others have been used as the basis for synthetic agents. These are potent and effective compounds, which have been obtained from plants, including anti-cancer (cytotoxic) agents, anti-malaria (anti-protozoal) agents, and anti-bacterial agents. Today, the number of plant families that have been extensively studied is relatively very few and the vast majorities have not been studied at all. The Annonaceae is the largest family in the order Magnoliales. It includes tropical trees, bushes, and climbers, which are often used as traditional remedies in Southeast Asia. Members of the Annonaceae have the particularity to elaborate a broad spectrum of natural products that have displayed anti-bacterial, anti-fungal, and anti-protozoal effects and have been used for the treatment of medical conditions, such as skin diseases, intestinal worms, inflammation of the eyes, HIV, and cancer. These special effects and the vast range of variation in potent compounds make the Annonaceae unique from other similar families in the Magnoliales and the Angiosperms in general. This paper attempts to summarize some important information and discusses a series of hypotheses about the effects of Annonaceae compounds.

Keywords: Annonaceae; alkaloids; flavonoids; acetogenins; lead compounds

1. Introduction

The order Magnoliales consists of six families (Annonaceae, Degeneriaceae, Eupomatiaceae, Himantandraceae, Magnoliaceae, and Myristicaceae), approximately 160 genera, and about more than 3000 species. Members of the Magnoliales include woody shrubs, climbers, and trees. Along with the orders Laurales, Piperales, and Canellales, Magnoliales forms the Magnoliid, which is an early evolutionary branch in the angiosperm tree [1,2]. Among all these families, the Annonaceae and Magnoliaceae have been the most studied. The family of Degeneriaceae consists of a single genus *Degeneria*, which has one or two species found in Fiji [3]. The family of Eupomatiaceae consists of the single genus, *Eupomatia*, including three species, found in New Guinea and eastern Australia [4]. The family Himantandraceae consists of the single genus, *Galbulimima*, which consists of two species found in the tropical Southeast Asia and Australia [5]. The Myristicaceae family consists of about 20 genera, with several 100 species, of trees and shrubs, found in the tropical areas across the world [6,7]. The Magnoliaceae family has approximately 225 species divided into

*Corresponding author. Email: khyxnai@nottingham.edu.my

ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020.2011.570265
http://www.informaworld.com

seven genera. This family is distributed across eastern North America, Mexico, Central America, the West Indies, tropical South America, southern and eastern India, Sri Lanka, Indochina, Malaysia, China, Japan, and Korea [8]. The barks of Magnolia species are highly aromatic on account of magnolol and honokiol, two polyphenolic compounds, which have demonstrated both anti-anxiety and anti-angiogenic properties. It has also been shown that these compounds are proven to have anti-inflammatory [9] and anti-oxidant [10] effects. The flower buds of Magnolia plants mainly contain monoterpenes and sesquiterpenes, which are decongestant, anti-inflammatory, and are used for commercial and domestic use [11]. In this family, compounds like lignans, neolignans, phenylpropanoids, terpenes, and some alkaloids, such as liriodenine, aporphine, and benzylisoquinoline alkaloids [12], have been isolated and they showed several biological activities [13–19].

The Annonaceae also called the custard apple family is the largest family in the Magnoliales order, with about 135 genera and 2500 species. The family is mainly concentrated in the tropical zones, with few species found in temperate regions [20]. One of the most important reason for focusing on Annonaceae is that there are different categories of chemicals such as alkaloids, non-alkaloids constituents, and acetogenins, which have displayed a broad array of pharmacological effects and are being clinically evaluated for the treatment of Parkinson's disease, cardiovascular disease, and viral infections [21,22]. Notwithstanding the existence of some other non-alkaloid compounds such as some sesquiterpenes like yingzhaosu A and yingzhaosu B with anti-malaria activity [23,24], there has been much more focus on flavonoids [25]. The occurrence of acetogenins in Annonaceae has turned this family on the spotlight to discover new anti-cancer agents. The aim of this study is to demonstrate that the family Annonaceae offers a vast array of leads to tomorrow's drug discovery.

2. Phytochemistry and pharmacology

2.1 Alkaloids

There are 150 alkaloids of the isoquinoline types, in which protoberberines and aporphines, which are structurally similar to each other, were isolated from different genera of Annonaceae [25]. Many pharmacological studies have indicated that bisbenzylisoquinolines that are derived from simple isoquinolines are important bioactive components existing in the family of the Annonaceae [26–32]; moreover, the tetrahydrobenzylisoquinoline alkaloids, which have a fully saturated and comparable structure to bisbenzylisoquinolines, perform an important function in biomedicine semi-synthetic productions. In addition, protoberberines and aporphine can be mentioned as the simplest derivatives of the bisbenzylisoquinolines and tetrahydrobenzylisoquinoline, respectively [33]. Therefore, we have described them in the following order: simple isoquinolines, benzyltetrahydroisoquinolines, bisbenzylisoquinolines, protoberberines, and aporphine.

2.1.1 Simple isoquinolines

Among the most promising simple isoquinolines isolated so far are salsolinol (Figure 1) from the leaf and stem of *Annona reticulata* [34], and corydaldine (Figure 2) from the stem bark of *Enantia polycarpa* [35]. Salsolinol had a considerable effect on the balance between

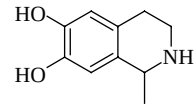

Figure 1. Chemical structure of salsolinol.

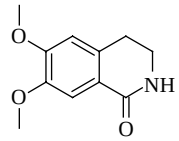

Figure 2. Chemical structure of corydaldine.

dopamine and acetylcholine by impairing the cholinergic system as well as the dopaminergic system. It is likely that the disruption of balance between dopamine and acetylcholine plays a critical role in the pathogenesis of neurotoxin-induced Parkinson's disease [36]. To sum up the previous studies, it is clear that salsolinol not only affects the dopaminergic system by inhibiting the related enzymes in the synthesis or metabolism of dopamine but also impairs the cholinergic system by inactivating acetylcholinesterase. Both phenomena would lead to the disruption of balance between dopamine and acetylcholine and contribute to the development of Parkinson's disease [37].

2.1.2 *Benzyltetrahydroisoquinolines*

Most benzyltetrahydroisoquinoline alkaloids (Figure 3) were isolated from some species of the genera *Annona* and *Xylopia*. One such compound is reticuline (Figure 4), which reduces heart rate and blood pressure in rats, inhibits phenylephrine- and KCl-elicited contractions of rat aortic rings, and antagonizes Ca^{2+}-induced contractions [38,39]. The reticuline inhibits the smooth muscle L-type Ca^{2+} channels. Reticuline elicits vasorelaxation via a probable blockade of the L-type voltage-dependent Ca^{2+} current in rat aorta [39].

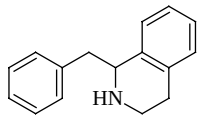

Figure 3. Structure of benzyltetrahydroisoquinoline.

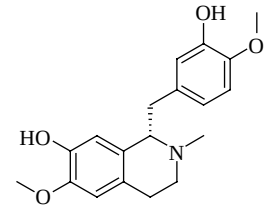

Figure 4. Chemical structure of reticuline.

2.1.3 *Bisbenzylisoquinolines*

These compounds have mostly been isolated from the genera *Crematosperma*, *Guatteria*, *Isolona*, *Phaeanthus*, *Popowia*, and *Uvaria*, and are very variable in structure (Figure 5) [40,41]. Bisbenzylisoquinolines are mainly Ca^{2+} antagonists, which have some effects on the vascular smooth muscle, the vascular endothelium, and the adrenal glands. They are also shown to have pro-apoptotic, anti-oxidant, and anti-inflammatory activities [42]. The most valuable characteristic of these compounds is their anti-plasmodial effect [43].

2.1.4 *Protoberberines*

Most protoberberine alkaloids have the basic skeleton as shown in Figure 6 [44]. These alkaloids have displayed an impressive array of pharmacological properties and are known for their anti-bacterial, anti-viral,

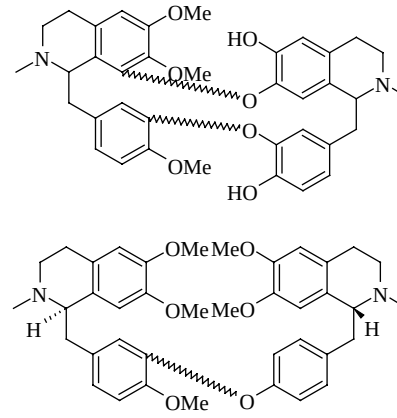

Figure 5. Structures of bisbenzylisoquinolines from Annonaceae.

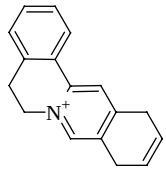

Figure 6. Basic skeleton of protoberberine alkaloids.

and cytotoxic activity. Palmatine and berberine inhibited the enzymatic activity of reverse transcriptase *in vitro* [45]. Furthermore, palmatine, berberine, jatrorrhizine, and dihydroberberine inhibited the growth of *Babesia gibsoni in vitro* at doses ranging from 1 to 100 μg/ml [46]. Protoberberine inhibited the growth of 38 human cancer cell lines [47].

2.1.5 *Aporphines*

An interesting feature of aporphines is their planar stereochemistry. One such compound is anonaine, which is the most frequently cited aporphine in the Annonaceae. Figures 7 and 8 illustrate the general structure of aporphines alkaloids and anonaine, respectively [48,49]. 7-Hydroxydehydrothalicsimidine, thalicsimidine, norpurpureine, lirinidine, and *N*-methylasimilobine from the leaves of *Annona purpurea* exhibited significant inhibition of arachidonic acid, collagen, and platelet-activating factor-induced platelet aggregation [50]. It is worth mentioning that aporphine alkaloids, especially those containing a 1,2-methylenedioxy group, are more potent against cancer cell lines [51].

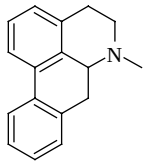

Figure 7. General structure of aporphine alkaloids.

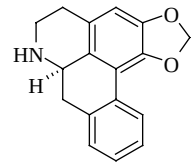

Figure 8. Structure of anonaine.

2.2 *Flavonoids*

More than 70 types of flavonoids have been reported from Annonaceae. In the flavanonol types, taxifoline has been reported frequently [52–54]. Among *ca.* 50 flavonols found in this family, quercetin types have broad pharmacological activities [55,56]. In addition, in the approximately 10 flavones, which have been isolated and studied, the *O*-glycosides of apigenin are common [54,56]. Therefore, in this study, the structures and bioactivities of taxifolin, apigenin-7-*O*-apiosyl (1 → 2) glycoside, and quercetin are discussed.

2.2.1 *Taxifolin*

Taxifolin or dihydroquercetin is a flavanonol (Figure 9). It is widespread in the Annonaceae [57]. Taxifolin is common in the Angiosperms and is known to be a potent anti-oxidant [58,59], anti-diabetic [60,61], anti-tumor [62–64], and anti-inflammatory [65] agent. Taxifolin provides reliable protection against environmental factors that cause arteriosclerosis, cardiac, hepatic, and pulmonary diseases. Taxifolin has also been proven to benefit cardiovascular health, the skin, cognitive function, inflammation, allergies, and immunodeficiency conditions, as well as the health of diabetics [66,67].

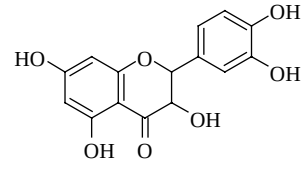

Figure 9. Structure of taxifolin.

2.2.2 Apigenin-7-O-apiosyl (1 → 2) glucoside

Apigenin-7-*O*-apiosyl (1 → 2) glucoside is a flavone found in *Artabotrys hexapetalus*, as shown in Figure 10 [56]. This flavonoid scavenges reactive oxygen species. Results obtained from *in vivo* and *in vitro* tests indicate that apigenin-7-*O*-apiosyl (1 → 2) glucoside is hepatoprotective. To sum up, further studies on the pharmaceutical functions and immunological responses of apigenin-7-*O*-apiosyl (1 → 2) glucoside may help its clinical application [68].

2.2.3 Quercetin

Quercetin (Figure 11) is a common flavonol in fruits, vegetables, leaves, and grains. It is used as an ingredient in supplements, beverages, or foods. In the Annonaceae, quercetin occurs in the leaves of *Annona glabra*, *Asimina triloba* [69], and *Annona senegalensis* [70]. Quercetin has demonstrated significant anti-inflammatory activity because of direct inhibition of several initial processes of inflammation. For instance, it easily inhibits both the manufacture and release of histamine and other allergic/inflammatory mediators. In addition, it exerts potent antioxidant activity and vitamin C-sparing action. Quercetin also has anti-tumor properties. A study in the *British Journal of Cancer* showed that, when treated with a combination of quercetin and ultrasound at 20 kHz for 1 min duration, skin and

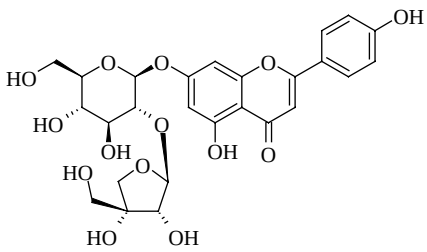

Figure 10. Structure of apigenin-7-*O*-apiosyl (1 → 2) glucoside.

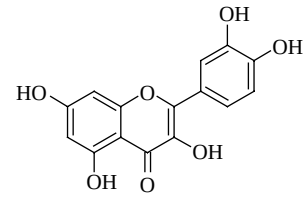

Figure 11. General structure of quercetin.

prostate cancers show 90% mortality within 48 h with no visible mortality of normal cells [71]. Recent studies have supported that quercetin can help men with chronic prostatitis, and both men and women with interstitial cystitis, possibly because of its action as a mast cell inhibitor [72]. Quercetin may have positive effects in combating or helping to prevent cancer, prostatitis, heart disease, cataracts, allergies/inflammations, and respiratory diseases such as bronchitis and asthma. It also has demonstrated anti-depressant properties [73]. Moreover, quercetin 3-rhamnoside (Figure 12) abrogates the replication of the influenza A virus by decreasing the synthesis of viral mRNAs [74]. Flavonoids of Annonaceae are extremely reactive toward free radicals and further investigations are warranted [75].

2.3 Acetogenins

The Annonaceae acetogenins are a unique class of secondary metabolites in plants. A literature survey indicated that more than 400 Annonaceae acetogenins have been isolated so far. This class of natural product displayed anti-cancer, cytotoxic,

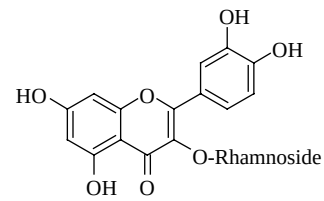

Figure 12. Structure of quercetin-3-*O*-rhamnoside.

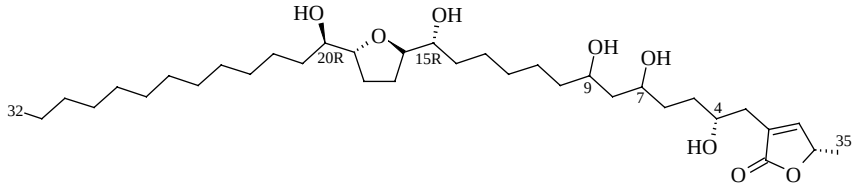

Figure 13. Structure of montalicin G.

anti-parasitic, insecticidal, and immunosuppressive effects and is regarded as a likely source for the development of potential drugs [76,77]. Therefore, it is vital to focus on the novel acetogenins such as montalicin G, asimicin, annonacine, uvaricin, purpuracenin, and annoglaucin.

2.3.1 *Montalicin G*

This acetogenin has been found exclusively in *Annona montana* (Figure 13). Montalicin G inhibited the growth of human tumor cell lines: MCF-7 (breast cancer), HCT-8 (ileocecal cancer), SK-MEL-2 (melanoma cancer), KB (epidermoid nasopharyngeal carcinoma), KB-VIN (vincristine-resistant KB), U-87-MG (glioblastoma cancer), CAKI (renal cancer), PC-3 (prostate cancer), as well as 1A9 (ovarian cancer), and PTX10 (ovarian cancer cell line with β-tubulin mutation), with ED_{50} values of 4.8, 11.5, 5.8, 12.7, 12.8, 9.2, 2.0, 3.5, 1.3, and 4.6 μg/ml, respectively [78].

2.3.2 *Asimicin*

Asimicin (Figure 14) was extracted from *Annona cornifolia*, *Annona bullata* and *A. triloba*, respectively [79]. This acetogenin showed anti-oxidant capacity comparable to vitamin C [80].

2.3.3 *Annonacin*

Annonacin (Figure 15) is found in the fruits of *Annona muricata* (soursop) [81]. Recent reports have shown that daily consumption in rats caused brain lesions leading to Parkinson's disease [82,83]. Along with other acetogenins, annonacin is reported to block mitochondrial complex I (NADH dehydrogenase), which is responsible for the conversion of NADH–NAD and the build-up of a proton gradient over the mitochondrial inner membrane. This effectively disables a cell's ability to generate ATP via an oxidative pathway, ultimately forcing a cell into apoptosis or necrosis [84].

2.3.4 *Uvaricin*

In 1982, a bis(tetrahydrofuranoid) fatty acid lactone called uvaricin (Figure 16) was isolated from *Uvaria accuminata* [85]. Uvaricin was the first in the cytotoxic acetogenins found in the Annonaceae. It kills cells by inhibiting NADH dehydrogenase in the mitochondrion [86].

2.3.5 *Purpuracenin and annoglaucin*

Purpuracenin (*cis*) and annoglaucin (*trans*) (Figure 17) have been isolated from *A. purpurea*. Purpuracenin and annoglaucin showed strong cytotoxic activity *in vitro* against MCF-7 (human breast carcinoma) and A-549 (human lung carcinoma) cell lines with ED_{50} 10, 1.56

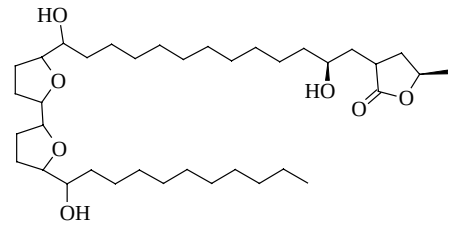

Figure 14. Structure of asimicin.

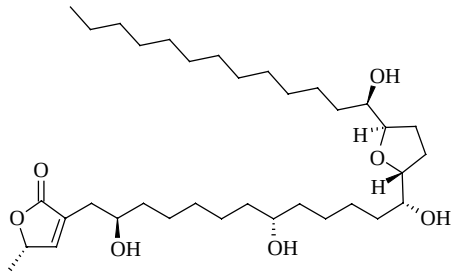

Figure 15. Structure of annonacin.

and 4.8×10^{-2}, 1.08 μg/ml, respectively [87].

3. Future development

Below are some hypotheses that are mentioned in three separated parts including alkaloids, flavonoids, and acetogenins, and they can be useful to feature new progressions in drug discovery.

3.1 Alkaloids

Salsolinol shares some chemical similarities with selegiline and has been modified in order to develop anti-Parkinson disease agents. Such compounds (Figure 18) are 1-methyl-1,2,3,4-tetrahydroisoquinoline (1-MeTIQ), 1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (1,3-diMeTIQ), and 1,3-dimethyl-*N*-propargyl-1,2,3,4-tetrahydroisoquinoline (1,3-diMe-*N*-proTIQ) [88]. Also based on the above review and the other original researches [89], it can be concluded that reticuline

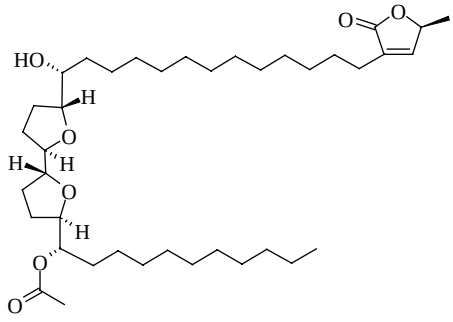

Figure 16. Structure of uvaricin.

can be mentioned as a chemical model for designing and subsequent developing of new drugs with cardiovascular-protective properties. In bisbenzylisoquinolines, the two moieties are usually bound by one or more diaryl ether bridges, although carbon–carbon bridges or a methyleneoxy bridge may also be present. Many studies show that the anti-plasmodial and cytotoxic effects of bisbenzylisoquinoline alkaloids are influenced by the configuration at chiral centers and by substituents on the aromatic rings. However, it was observed that a decrease in lipophilicity, as in quaternarized or *N*-oxide derivatives, resulted in the loss of both toxicity and anti-plasmodial activity. This loss was probably a consequence of altered membrane permeability [90]. A modification of the aromatic rings with lipophilic moieties should increase the anti-plasmodial effects of the drug. The ability of the protoberberines to act as a poison against topoisomerase-I (Topo-I) and topoisomerase-II (Topo-II) has been related to their anti-tumor activity [91,92]. Inhibitors of the enzyme Topo-II have been studied more frequently than those of Topo-I and the principal mechanisms of inhibition of Topo-II have been discovered. However, the role of the drug–DNA interactions in Topo-I inhibition is still unclear, although the binding of the protoberberine to DNA has been considered to be responsible for this activity. Three principal noncovalent modes of binding small ligands to oligonucleotides can be distinguished: (a) external binders, often polyamines that make nonspecific electrostatic contacts with the DNA backbone; (b) minor groove binders, the most sequence-selective class, regards to a network of specific H-bonds to base-pairs and backbone functions; and (c) base-pair intercalators that establish extended and partly specific van der Waals contacts with the floors of aromatic pairs [93]. Therefore, it is anticipated that by considering these issues and using molecular modeling

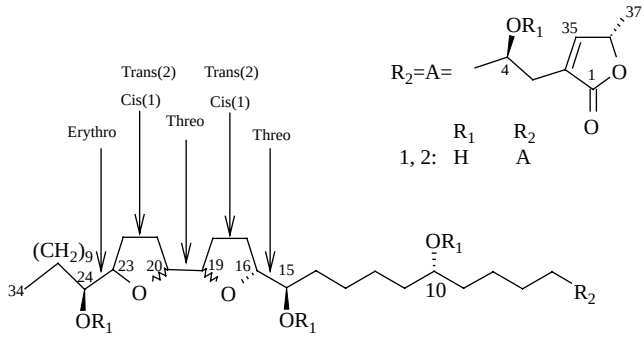

Figure 17. Structures of purpuracenin and annoglaucin.

(simulation of the obtained alkaloids with these structures to Topo I and II enzymes), we can design novel semi-synthetic medicines. Previous studies on aporphines suggest that it may be possible to modulate the biological activities of some agents such as liriodenine through some modifications to improve the DNA intercalation (Figure 19) [94].

3.2 *Flavonoids*

The apigenin-7-*O*-apiosyl (1 → 2) glucoside and derivatives are potent hepatoprotective agents *in vitro*, but no data are available *in vivo*. Based on the modeling and docking studies between apigenin-7-*O*-apiosyl (1 → 2) glucoside and human serum albumin (the main transporter in blood), hydrophobic and electrostatic forces play important role in the interaction between apigenin-7-*O*-apiosyl (1 → 2) glucoside and human serum albumin [95]. Also regarding the interactions, it is clear that by modifying the lipophilic groups, the charge transfer interaction between apigenin-7-*O*-apiosyl (1 → 2) glucoside and human serum albumin will improve and hydrogen bonding can also be stronger by adding some polar groups such as hydroxyl and amine [95]. To sum up, these studies provide some valuable information for the transportation and distribution of apigenin-7-*O*-apiosyl (1 → 2) glucoside *in vivo* and are helpful for clarifying toxicity and dynamics of apigenin-7-*O*-apiosyl (1 → 2) glucoside. Influenza viruses are enveloped RNA viruses that belong to the family orthomyxoviridae causing significant morbidity and mortality in humans through epidemics or pandemics. Influenza virus spreads from person to person via the aerosol route, which is generally highly efficient and often difficult to control as evident from the recent swine flu outbreak. Anti-viral agents can prevent and treat influenza infection, even in the event that

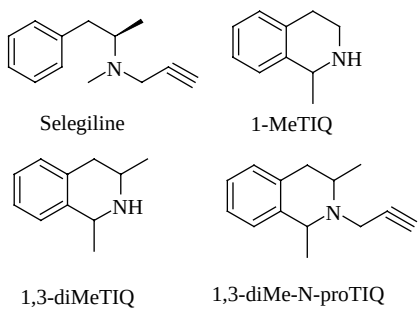

Figure 18. The structures of selegiline, 1-MeTIQ, 1,3-diMeTIQ, and 1,3-diMe-*N*-proTIQ.

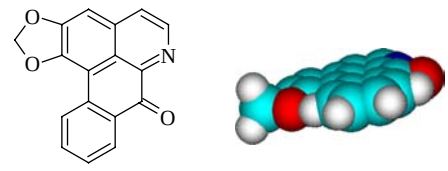

Figure 19. Chemical structure and the space-filling model of planar conformation of liriodenine.

an epidemic strain has undergone a significant change in its antigenic structure that is no longer covered by the current vaccine. So it is worth noticing that quercetin-3-rhamnoside has superior anti-influenza activity over oseltamivir (Tamiflu) [74]. Therefore, it is expected that using rational drug design method, we can produce its heterocyclic analogues as potential new classes of anti-influenza compounds.

3.3 Acetogenins

The Annonaceae acetogenins represent a class of compounds with diverse bioactivities, including promising cytotoxicities [96]. The Annonaceae acetogenins have been shown to be potent inhibitors of complex I (NADH: ubiquinone oxidoreductase) of mitochondrial electron transport systems (ETS) [97–99]. It is believed that they cause tumor cell inhibition by blocking oxidative phosphorylation, and therefore limiting the level of ATP, inducing a type of suffocation (ATP deprivation) at the cellular level. Recently, it has been shown that the acetogenins selectively inhibit the NADH oxidase activity of plasma membrane vesicles derived from HeLa (human cervical carcinoma), HL-60 (human promyelocytic leukemia), and HL-60/Adr (human promyelocytic leukemia resistant to adriamycin) cells while not affecting those derived from normal rat liver cells. This second mode of action also lowers intracellular ATP levels by blocking NAD regeneration and, thus, inhibiting glycolytic (substrate level) phosphorylation in the cytosol; these combined modes of action likely lead to apoptosis (programed cell death) [100,101]. The selectivity of the acetogenins for tumor cells could then be explained both by the higher activities of the NADH oxidase that are peculiar to tumor cells as well as the increased ATP demands that are inherent due to their uncontrolled growth. Studies have hypothesized that since acetogenins lower intracellular ATP levels, they may be effective in circumventing multi-drug resistance (MDR) [100,101]. Taken together, these results suggest that acetogenins show considerable promise for the development of new anti-neoplastic agents, with excellent potential for the treatment of multi-drug resistance tumor. In another study, 14 acetogenins were tested in a rat liver mitochondrial oxygen uptake assay to probe additional structure–activity relationships. In this subcellular assay, the activity of nonadjacent bis-tetrahydrofuran ring acetogenins depends on the distance between the two tetrahydrofuran rings; the activity decreases to that of a monotetrahydrofuran ring acetogenin if the distance is too long. When one tetrahydrofuran ring is replaced with a tetrahydropyran ring, the activity remains comparable. The configuration of the tetrahydrofuran ring, in mono-ring compounds, seems to be more important than stereo-chemical differences in the rings of adjacent bis-tetrahydrofuran ring compounds [96]. In conclusion, it is anticipated that novel acetogenins structures may play a key role in chemotherapy.

4. Conclusion

The above review indicates that the literature on Annonaceae has grown considerably in the last decade and a vast field is now open for in-depth investigations. All in all, among the alkaloids, isoquinolines are reminded to be crucial agents. They possess anti-bacterial and anti-protozoal activity. In addition, alkaloids have the anti-inflammatory effect. Totally, Annonaceae alkaloids play key roles in folk treatments. About the flavonoids, the anti-oxidant activity is the most noticeable part. Regarding acetogenins, it is undoubtedly true that these agents give the Annonaceae its unique characteristics. Acetogenins have exhibited anti-cancer, anti-oxidant, and anti-HIV activities at very low concentrations and, therefore, these agents can cause less side effects.

It is possible that chemical modification of these lead compounds may soothe the way to new pharmacologically selective and therapeutically potent ideal medicines. The discovery of leads from the Annonaceae is most probable.

References

[1] Angiosperm Phylogeny Group, *Bot. J. Linn. Soc.* **141**, 399 (2003).

[2] P.S. Soltis and D.E. Soltis, *Am. J. Bot.* **91**, 1614 (2004).

[3] L. Watson and M.J. Dallwitz, *Degeneriaceae, The Families of Flowering Plants: Descriptions, Illustrations, Identification, and Information Retrieval* (April 2006), 2nd Version. <http://delta-intkey.com>.

[4] L. Watson and M.J. Dallwitz, *Eupomatiaceae, The Families of Flowering Plants: Descriptions, Illustrations, Identification, Information Retrieval* (May 2006), 3rd Version. <http://delta-intkey.com>.

[5] L. Watson and M.J. Dallwitz, *Himantandraceae, The Families of Flowering Plants: Descriptions, Illustrations, Identification, Information Retrieval* (May 2006), 3rd Version. <http://delta-intkey.com>.

[6] L. Watson and M.J. Dallwitz, *Myristicaceae, The Families of Flowering Plants: Descriptions, Illustrations, Identification, Information Retrieval* (May 2006), 3rd Version. <http://delta-intkey.com>.

[7] H. Sauquet and T. Le, *Int. J. Plant Sci.* **164**, 613 (2003).

[8] W.B. Zomlefer, *Guide to Flowering Plant Families* (The University of North Carolina Press, USA, 1994).

[9] H.J. Son, H.J. Lee, H.S. Yun-Choi, and J.H. Ryu, *Planta Med.* **66**, 469 (2000).

[10] Y. Caia, Q. Luob, M. Sunc, and H. Corkea, *Life Sci.* **74**, 2157 (2004).

[11] D. Hunt, *Magnolias and their Allies* (International Dendrology Society and Magnolia Society, England, 1998).

[12] B. Talapatra, P.K. Chaudhuri, and S.K. Talapatra, *Phytochemistry* **21**, 747 (1982).

[13] M.A. Kelm and M.G. Nair, *Stud. Nat. Prod. Chem.* **24**, 845 (2000).

[14] D. Warthen, E.L. Gooden, and M. Jacobson, *J. Pharm. Sci.* **58**, 637 (1968).

[15] A. Villar, M. Mares, J.L. Rios, E. Canton, and M. Gobernado, *Pharmazie* **42**, 248 (1987).

[16] L.A. Martinez, J.L. Rios, M. Paya, and M.J. Alcaraz, *Free Rad. Biol. Med.* **12**, 287 (1992).

[17] I.L. Tsai, Y.F. Liou, and S.T. Lu, *Kaohsiung J. Med. Sci.* **5**, 132 (1989).

[18] M.Q. Paulo, J.M. Barbosa-Filho, E.O. Lima, R.F. Maia, R.C. Barbosa, and M.A. Kaplan, *J. Ethnopharmacol.* **36**, 39 (1992).

[19] A. Ubeda, C. Montesinos, M. Payá, and M.J. Alcaraz, *Free Rad. Biol. Med.* **15**, 159 (1993).

[20] J.E. Richardson, L.W. Chatrou, J.B. Mols, R.H.J. Erkens, and M.D. Pirie, in *Flowering Plants of the Neotropics*, edited by N. Smith, S.A. Mori, A. Henderson, D.W. Stevenson, and S.V. Healdet (Princeton University Press, Princeton, NJ, 2004).

[21] M. Cuendet, C.P. Oteham, R.C. Moon, W.J. Keller, P.A. Peaden, and J.M. Pezzuto, *Pharm. Biol.* **46**, 3 (2008).

[22] A. Suedee, I.O. Mondranondra, A. Kijjoa, M. Pinto, N. Nazareth, M.S.J. Nascimento, A.M.S. Silva, and W. Herz, *Pharm. Biol.* **45**, 575 (2007).

[23] X.T. Liang, D.Q. Yu, W.L. Wu, and H.C. Deng, *Acta Chim. Sin.* **37**, 215 (1979).

[24] X.T. Liang, D.Q. Yu, and W.D. Pan, *Acta Chim. Sin.* **37**, 231 (1979).

[25] M. Leboeuf, A. Cave, P.K. Bhaumik, B. Mukherjee, and R. Mukherjee, *Phytochemistry* **21**, 2783 (1982).

[26] A. Fournet, A.A. Barrios, V. Muíioz, R. Hocquemiller, and A. Cave, *Phytother. Res.* **7**, 281 (1993).

[27] C.P. Munshi, P.M. Vaidya, J.J. Buranpuri, and O.D. Gulati, *J. Indian Med. Assoc.* **59**, 287 (1972).

[28] A.R. de Arias, A. Inchausti, M. Ascurrat, N. Fleitas, E. Rodriguez, and A. Fournet, *Phytother. Res.* **8**, 141 (1994).

[29] K. Likhitwitayawuid, C.K. Angerhofer, G.A. Cordell, and J.M. Pezzuto, *J. Nat. Prod.* **56**, 30 (1993).

[30] A. Valentin, F. Benoit-Vical, C. Moulis, E. Stanislas, M. Mallié, I. Fouraste, and J. Bastide, *Antimicrob. Agents Chemother.* **41**, 2305 (1997).

[31] C.K. Angerhofer, H. Guinaudeau, V. Wongpanich, J.M. Pezzuto, and G.A. Cordell, *J. Nat. Prod.* **62**, 59 (1999).

[32] J.D. Phillipson, M.F. Roberts, and M.H. Zenk, *The Chemistry and Biology of*

Isoquinoline Alkaloids (Springer, New York, 1985), pp. 81–86.
[33] D.S. Siegler, *Plant Secondary Metabolism* (Springer, New York, 2001), pp. 584–587.
[34] A. Touché, J.F. Desconclois, H. Jacquemin, Y. Lelièvre, and P. Forgacs, *Planta Med. Phytoth.* **15**, 4 (1981).
[35] A. Jossang, M. Leboeuf, A. Cavé, M. Damak, and C. Riche, *Planta Med.* **32**, 249 (1977).
[36] W. Zhu, D. Wang, J. Zheng, Y. An, Q. Wang, W. Zhang, L. Jin, H. Gao, and L. Lin, *Clin. Chem.* **54**, 705 (2008).
[37] H. Soreq and S. Seidman, *Nat. Rev. Neurosci.* **2**, 294 (2001).
[38] G. Aguilar-Santos, J.R. Librea, and A.C. Santos, *Philipp. J. Sci.* **96**, 399 (1967).
[39] M.A. Medeiros, X.P. Nunes, J.M. Barbosa-Filho, V.S. Lemos, J.F. Pinho, D. Roman-Campos, I.A. Medeiros, D.A. Araújo, and J.S. Cruz, *Naunyn Schmiedeberg's Arch.* **379**, 115 (2009).
[40] P.E. Sonnet and M.J. Jacobson, *Pharm. Sci.* **60**, 1254 (1971).
[41] M. Leboeuf, F. Bévalot, and A. Cavé, *Planta Med.* **38**, 33 (1980).
[42] C.Y. Kwan and F.I. Achike, *Acta Pharmacol. Sin.* **23**, 1057 (2002).
[43] I. Kitagawa, K. Minagawa, R.S. Zhang, K. Hori, M. Doi, M. Inoue, T. Ishida, M. Kimura, T. Uji, and H. Shibuya, *Chem. Pharm. Bull.* **41**, 997 (1993).
[44] P.G. Waterman and K. Pootakahm, *Planta Med.* **37**, 247 (1979).
[45] L. Manohar, *J. Pharm. Sci.* **72**, 538 (1983).
[46] H. Matsuura, K. Takahashi, M. Yamasaki, O. Yamato, and Y. Maede, *J. Vet. Med. Sci.* **67**, 223 (2005).
[47] K. Iwasa, M. Moriyasu, T. Yamori, T. Turuo, D.U. Lee, and W. Eiegrebe, *J. Nat. Prod.* **64**, 896 (2001).
[48] G. Barger and L.J. Sargent, *J. Chem. Sot.* 991 (1939).
[49] E. Schlittler and H.U. Huber, *Helv. Chim. Acta* **35**, 111 (1952).
[50] F. Chang, J. Wei, C. Teng, and Y. Wu, *Phytochemistry* **49**, 2015 (1998).
[51] D.B. da Silva, E.C. Tulli, G.C. Militão, L.V. Costa-Lotufo, C. Pessoa, M.O. de Moraes, S. Albuquerque, and J.M. de Siqueira, *Phytomedicine* **16**, 1059 (2009).
[52] T. Li and J. Yu, *Acta Pharm. Sin.* **33**, 591 (1998).
[53] R. Gonda, T. Takeda, and T. Akiyama, *Chem. Pharm. Bull.* **48**, 1219 (2000).
[54] T.M. Li, W.K. Li, and J.G. Yu, *Phytochemistry* **45**, 831 (1997).
[55] C.M. Hu, *China J. Chin. Mater. Med.* **32**, 765 (2009).
[56] D.Y.A.C. Santos and M.L.F. Salatino, *Phytochemistry* **55**, 567 (2000).
[57] M.B. Plotnikov, O.I. Aliev, M.J. Maslov, A.S. Vasiliev, and N.A. Tjukavkina, *Phytother. Res.* **17**, 276 (2003).
[58] A.K. Ratty, J. Sunammoto, and N.P. Das, *Biochem. Pharmacol.* **37**, 989 (1988).
[59] H. Haraguchi, Y. Mochida, S. Sakai, H. Masuda, and Y. Tamura, *Biosci. Biotechnol. Biochem.* **60**, 945 (1996).
[60] H. Haraguchi, I. Ohmi, A. Fukuda, Y. Tamura, K. Mizutani, O. Tanaka, and W.H. Chou, *Biosci. Biotechnol. Biochem.* **61**, 651 (1997).
[61] N.P. Nanayakkara, R.A. Hussain, J.M. Pezzuto, D.D. Soejarto, and A.D. Kinghorn, *J. Med. Chem.* **31**, 1250 (1988).
[62] S.C. Chu, Y.S. Hsieh, and J.Y. Lin, *J. Nat. Prod.* **55**, 179 (1992).
[63] C. Kandaswami, E. Perkins, G. Drzewiecki, D.S. Soloniuk, and E.J. Middleton, *Anticancer Drugs* **3**, 525 (1992).
[64] M.A. Devia and N.P. Das, *Cancer Lett.* **69**, 191 (1993).
[65] M.B. Gupta, T.N. Bhalla, G.P. Gupta, C.R. Mitra, and K.P. Bhargava, *Jpn J. Pharmcol.* **21**, 377 (1971).
[66] J.Q. Gu, S. Ikuyama, P. Wei, B. Fan, J. Oyama, T. Inoguchi, and J. Nishimura, *Am. J. Physiol. Endocrinol. Metab.* **295**, 390 (2008).
[67] J.Y. Ahn, S.E. Choi, M.S. Jeong, K.H. Park, N.J. Moon, S.S. Joo, C.S. Lee, Y.W. Choi, K. Li, M.K. Lee, M.W. Lee, and S.J. Seo, *Phytother. Res.* **24**, 1071 (2010).
[68] Q.S. Zheng, X.L. Sun, B. Xu, G. Li, and M. Song, *Biomed. Environ. Sci.* **18**, 65 (2005).
[69] R. Hegnauer, *Chemotaxonomie der Pflanzen* (Birkhäuser, Basel, 1964), Vol. 3, pp. 166–167.
[70] A. MacKie and N. Ghatge, *J. Sci. Food Agric.* **9**, 88 (1958).
[71] R.D. Gibbs, *Chemotaxonomy of Flowering Plants* (McGill-Queen's University Press, Montreal, 1974).
[72] S. Paliwal, J. Sundaram, and S. Mitragotri, *Br. J. Cancer* **92**, 499 (2005).
[73] D.A. Shoskes, S.I. Zeitlin, A. Shahed, and J. Rajfer, *Urology* **54**, 960 (1999).
[74] H.J. Choi, J.H. Song, K.S. Park, and D.H. Kwon, *Eur. J. Pharm. Sci.* **37**, 329 (2009).

[75] P.C. Hollman and M.B. Katan, *Food Chem. Toxicol.* **37**, 937 (1999).
[76] I.B. Ndob, P. Champy, C. Gleye, G. Lewin, and B. Akendengué, *Phytochem. Lett.* **2**, 72 (2009).
[77] Y. Nakanishi, F.R. Chang, C.C. Liaw, Y.C. Wu, K.F. Bastow, and K.H. Lee, *J. Med. Chem.* **46**, 3185 (2003).
[78] C.C. Liaw, F.R. Chang, S.L. Chen, C.C. Wu, K.H. Lee, and Y.C. Wu, *Bioorg. Med. Chem.* **13**, 4767 (2005).
[79] J.K. Rupprecht, Y.H. Hui, and J.L. McLaughlin, *J. Nat. Prod.* **53**, 237 (1990).
[80] L.A.R. Santos Lima, L.P.S. Pimenta, and M.A.D. Boaventura, *Food Chem.* **122**, 1129 (2010).
[81] F.E. Wu, G.X. Zhao, L. Zeng, Y. Zhang, J.T. Schwedler, J.L. McLaughlin, and S. Sastrodihardjo, *J. Nat. Prod.* **58**, 1430 (1995).
[82] A. Lannuzel, P.P. Michel, G.U. Höglinger, P. Champy, A. Jousset, F. Medja, A. Lombès, F. Darios, C. Gleye, A. Laurens, R. Hocquemiller, E.C. Hirsch, and M. Ruberg, *Neuroscience* **121**, 287 (2003).
[83] P. Champy, G.U. Höglinger, J. Féger, C. Gleye, R. Hocquemiller, A. Laurens, V. Guérineau, O. Laprévote, F. Medja, A. Lombès, P.P. Michel, A. Lannuzel, E.C. Hirsch, and M. Ruberg, *J. Neurochem.* **88**, 63 (2004).
[84] J.L. McLaughlin, *J. Nat. Prod.* **71**, 1311 (2008).
[85] S.D. Jolad, J.J. Hoffmann, K.H. Schram, J.R. Cole, M.S. Tempesta, G.R. Kriek, and R.B. Bates, *J. Org. Chem.* **47**, 3151 (1982).
[86] M.C. Zafra-Polo, M.C. Gonzales, E. Estornell, S. Sahpaz, and D. Cortes, *Phytochemistry* **42**, 253 (1996).
[87] D. Chavez and R. Mata, *Phytochemistry* **50**, 823 (1999).
[88] K. Nobuyuki, C. Satomi, A. Kenji, N. Hiroshi, K. Michikaz, H. Keiko, H. Yoshie, and T. Kyoji, *Brain Res.* **1321**, 133 (2010).
[89] K.L. Dias, D.C. da Silva, J.M. Barbosa-Filho, R.N. Almeida, C.N. de Azevedo, and I.A. Medeiros, *Planta Med.* **70**, 328 (2004).
[90] K. Kirandeep, J. Meenakshi, K. Tarandeep, and J. Rahul, *Bioorg. Med. Chem.* **17**, 3229 (2009).
[91] S.A. Kim, Y. Kwon, J.H. Kim, M.T. Muller, and I.K. Chung, *Biochemistry* **37**, 16316 (1998).
[92] S. Mazzini, M.C. Bellucci, and R. Mondelli, *Bioorg. Med. Chem.* **11**, 505 (2003).
[93] S. di Micco, C. Bassarello, G. Bifulco, R. Riccio, and L. Gomez-Paloma, *Angew Chem. Int. Ed.* **45**, 224 (2006).
[94] S.H. Woo, N.J. Sun, J.M. Cassady, and R.M. Snapka, *Biochem. Pharmcol.* **57**, 1141 (1999).
[95] J.L. Yuan, Z. Lv, Z.G. Liu, Z. Hu, and G.L. Zou, *J. Photoch. Photobiol. A* **191**, 104 (2007).
[96] D. Alfonso, H.A. Johnson, T. Colman-Saizarbitoria, C.P. Presley, G.P. McCabe, and J.L. McLaughlin, *Nat. Toxins* **4**, 181 (1996).
[97] K.I. Ahammadsahib, R.M. Hollingworth, J.P. McGovren, Y.H. Hui, and J.L. McLaughlin, *Life Sci.* **53**, 1113 (1993).
[98] M.A. Lewis, J.T. Arnason, B.J.R. Philogene, J.K. Rupprecht, and J.L. McLaughlin, *Pesticide Biochem. Physiol.* **45**, 15 (1993).
[99] M. Londershausen, W. Leicht, F. Lieb, H. Moeshler, and H. Weiss, *Pesticide Sci.* **33**, 427 (1991).
[100] X.P. Fang, M.J. Rieser, Z.M. Gu, G.X. Zhao, and J.L. Mclaughlin, *Phytochem. Anal.* **4**, 27 (1993).
[101] Z.M. Gu, G.-X. Zhao, N.H. Oberlies, L. Zeng, and J.L. McLaughlin, in *Recent Advances in Phytochemistry*, edited by J.T. Romeo (Plenum Press, New York, 1995), pp. 249–310.