Plant Derived Compounds Having Activity against P388 and L1210 Leukemia Cells

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Abstract

Cancer is a major cause of death and the number of new cases as well as the number of individuals living with cancer is expanding continuously. Due to the enormous propensity of plants that synthesize mixture of structurally derived bioactive compounds, the plant kingdom is potentially diverse source of chemical constituents with murine leukemia activity. Plant derived compounds have played an important role in the development of several clinically useful anticancer agents having activity against murine leukemia. These include vinca alkaloids, lignans, terpenoids, quinines and phytochemicals such as flavones, flavonoids, flavonol. The active compounds which have been isolated from various plant sources are listed, classified and discussed in terms of their activity against murine leukemia cells. Structure-activity relationship has been studied for further development of compounds which show activity against leukemia cells.

Keywords: Plant sources; active compounds; anticancer; murine; L1210; P388; leukemia cells.

1. Introduction

Plant products have been shown to be a valuable source of novel anticancer drugs for the treatment of various types of leukemia. We know that cancer is one of the most serious health problems all over the world. Significant progress in the development of novel drugs and therapies has occurred within the last 60 years and, thanks to the discovery of drugs such as Cisplatin, the taxanes and the nitrogen mustard in the last century, treatment of some forms of the disease has a high success rate, although patients must often tolerate unpleasant side effects [1]. Only in the last decade has there been some success in developing "targeted" drugs and therapies with fewer side effects [2]. For example, the recent discovery and rapid licensing of Imatinib (Gleevec ^{TM}) for the treatment of chronic myelogenous leukemia is often heralded as the start of a new era in the development of noncytotoxic agents targeted toward distinct biological pathways [1]. Murine leukemia virus: There are mainly three types of this virus. (i) Moloney murine leukemia virus [3]. (ii) Abelson murine leukemia virus [4, 5]. (iii) Feline leukemia virus. These belong to retroviruses. From application point of view, Murine leukemia virus (MuLV) can be used to study cancer mutagenesis. Various compounds, isolated from different plant sources, are divided into different types for the development of new drug compounds having activity against murine leukemia [6].

2. Alkaloids

They are widely distributed in the plant kingdom and many of them are active against KB cells or walker 256 carcinoma. Indicine-N-oxide (1) (Figure 1): It is isolated from *Helotropium indicum* L, possesses activity against P388 and L1210 leukemia [7, 8]. It was entered into clinical trials. Hepatotoxicity commonly associated with this class of alkaloids may not be a clinical problem with this compound [6]. *Helotropium indicum* has been used against warts and it is close relative *H. europaeum* L., has already been well recommended for the treatment of cancer [6]. Camptothecin (2) (Figure 1) a novel structure isolated in minute quantity from the wood of *Camptotheca acuminata Decne*, is highly active in P388 and L1210 leukemia but causes gastrointestinal tract toxicity in mouse [6, 9, 10]. A number of Camptothecin analogues are currently being developed as anticancer agents. Camptothecin was established as having in vivo activity against murine leukemia and rat walker 256 carcinosarcoma models [1]. While clinical trials on the parent alkaloid and Camptothecin sodium was not

particularly successful due to toxicity problems, interest in Camptothecin intensified once it was discovered that it exhibits a novel mechanism of action by inhibiting the enzyme DNA topoisomerase I [1]. Accordingly, a number of Camptothecin analogues have been developed in an attempt to reduce toxicity, optimize efficacy and improve water solubility without opening the lactone ring present in the parent molecule [11]. It was reported that Camptothecin as an inducer of cell differentiation [12]. Emetine dihydrochloride (3) (Figure 1) has been isolated from *Cephaelis acuminata karst*. It has already used as an ambebicide, an old commercial drug. It was entered to clinical trial on the basis of its activity in P388 and L1210 leukemias. Moreover, it is isoquinoline alkaloids [13] originally isolated from Rubiaceae family grow in South America and Asia [14].

Harringtonine and homoharringtonine (4) (Figure 1): These alkaloids, together with isoharringtonine, isolated from *Cephalotaxus harringtonia R. Sm. var. drupacea* from a type of active alkaloid which consists of complex esters of the inactive alcohol Cephalotaxine [6, 15]. It has shown efficacy against various myelogenous leukemias [16] (Figure 1). Cryptolepine and neocryptolepine (5, 5a) (Figure 2) are derivatives of indoloquinoline isolated from the roots of the African plant *Cryptolepis sanguinolenta*. These two alkaloids have potent cytotoxic activity against P388 and HL-60 cells. Mechanistic study of them showed that Cryptolepine is four times more toxic than neocryptolepine. This indicated that two nitrogen atoms on the same side of chromophore [17]. This study suggests the development of new cellular target for alkaloids instead of topoisomerases-II. Berberine (6) (Figure 2) is an isoquinoline alkaloid commonly used in both China and other countries as botanical drug present in Berberidaceae, Ranuculaceae, Papaveraaceae. It inhibits the N-acetyltranferase, cyclooxygenase-2 (COX-2) and topoisomerases. It demonstrated anticancer activity against various WEHI-3 leukemia cells [18]. Mechanism of its action has been the induction of apoptosis via activation of caspase-3 and inhibition of topoisomerases-II [19]. Vinorelbine (7) (Figure 1) is novel semisynthetic analogue of vinca alkaloid. With reference to the activity of Vinorelbine against P388 and L1210 leukemia, it showed activity against breast cancer, having more advantages over Cisplatin [16, 20]. Other vinca alkaloids are isolated from the Madagascar periwinkle, *Catharanthus roseus* G. Don (formerly named as *Vinca rosea* L) [21]. Sanguinarine (8) (Figure 1) produce a dose dependent increase in DNA damage and cytotoxicity in both primary mouse spleen cells and L1210 cells [22]. Cytotoxic activities of Sanguinarine and dihydrosanguinarine against HL-60 leukemia cells have also been reported. Chelidonin (9) isolated from *Chelidonium majus* did not show significant cytotoxicity or damage to DNA but completely arrested growth of L1210 cells [23].

3. Terpenes

This is a large and complex group of natural products. Linalool (10) (Figure 2), a natural monoterpene found in *Lavendula officinalis* [24] possesses antitumor activity against several human tumor cell lines. It is also an ingredient of many plants such as *Coriander sativum*, *Laurus nobilis* and *Myristica fragans* and of other plants. Effect of linalool on various leukemia cells led to strong activation of p53, cyclin dependent kinase inhibitors. This result suggests a path of induction of apoptosis. Thus, linalool acts as lead compound for the development of new therapeutic agents for murine and human leukemia [25]. A majority of the compounds of sesquiterpenes have cytotoxicity against KB, P388 leukemia (in vivo). A few of them have activity against walker 256. A large number of compounds showed activity in vivo against P388 leukemia cells although none has shown activity in L1210 as yet [6]. Researchers have developed new sesquiterpenes having activity against murine leukemia and human leukemia cell lines. Wilfortrine (11) (Figure 2) has already reported that growth of murine leukemia cell (in vivo) is inhibited by Sesquiterpenes alkaloid. Wilfortrine found it in *Tripterygium wilfordii hook* (also called the thunder god vine) [26, 27]. Diterpenes: This subgroup has yielded two compounds of highly activity in P388 leukemia. Triptolide (12) (Figure 2) is also active in L1210 leukemia. SAR study of diterpenoids from *Perovskia abrotanoides* and its semisynthetic analogues have been shown against P388 murine leukemia cells [28]. Diterpene ketones such as 5, 9-syn-rosanes Petalostigmones A and B, the erythroxylane Petalostigmones C, the norditerpene lactone Pubescenone and the (-)-Sonderianol are isolated from *Petalostigma pubescens*. Out of these, Sonderianol (13) (Figure 2) showed highest activity against mouse leukemia L1210 and P388 cells [29]. Triterpenes Cucurbitacins (14) (Figure 2) as a class show general cytotoxicity and negative or marginal in vivo antitumor activity against P388 leukemia, L1210 leukemia, B16 melanoma and Lewis lung tumor. Other triterpenes are not cytotoxic but show activity against walker 256 [6]. Semisynthetically derived novel triterpenoid AMR-Me (15) (Methyl-25-hydroxy-3-oxoolean-12-en-28 oate) (Figure 2) has inhibited telomerase activity in human leukemia CEM cells [30].

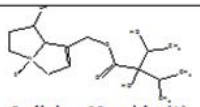
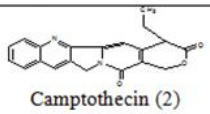
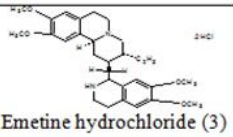
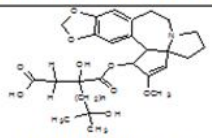
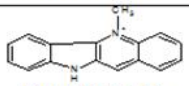
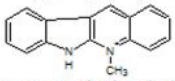
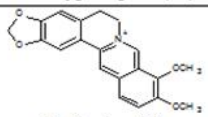
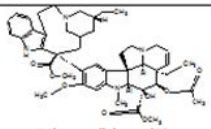
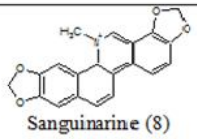
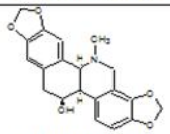
Alkaloids			
No.	Structure & Name	Sources	Activities
1	 Indicine-N-oxide (1)	 *Helotropium indicum L*	P388 and L1210 leukemia
2	 Camptothecin (2)	 *Camptotheca acuminata*	P388 and L1210 leukemia
3	 Emetine hydrochloride (3)	 *Cephaelis acuminata*	P388 and L1210 leukemia
4	 Harringtonine n=2 Homoharringtonine n=3 (4)	 *Cephalotaxus harringtonia R. Sm. var. drupacea*	Myelogenous leukemias
5	 Cryptolepine (5)  Neocryptolepine (5a)	 *Cryptolepis sanguinolenta*	P388 and HL-60 cells
6	 Berberine (6)	 *Berberis darwinii*	WEHI-3 leukemia cells
7	 Vinorelbine (7)	 *Catharanthus roseus G. Don*	P388 and L1210 leukemia
8	 Sanguinarine (8)	 *Sanguinaria canadensis*	Primary mouse spleen cells, L1210 cells & HL-60 leukemia cells
9	 Chelidonin (9)	 *Chelidonium majus*	L1210 leukemia

Figure 1. Structures, plant sources & activities of Alkaloids.

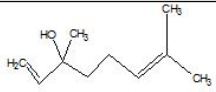
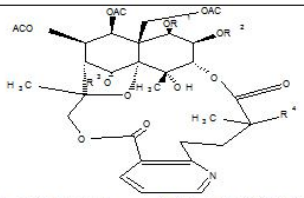
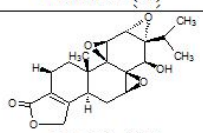
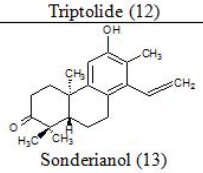
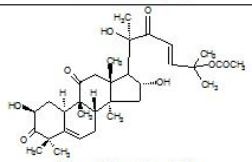
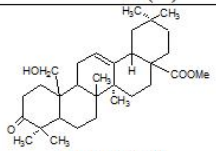
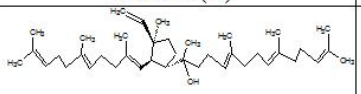
Terpenes			
No.	Structure & Name	Sources	Activities
1	 Linalool (10)	 *Lavendula officinalis*	In vivo P388 leukemia
2	 R^1=AC, R^2=3-furanoyl, R^3=AC & R^4=OH. Wilfortrine (11)	 *Tripterygium wilfordii hook*	In vivo P388 and L1210 leukemia
3	 Triptolide (12)	 *Cephaelis acuminata*	L1210 leukemia
4	 Sonderianol (13)	 *Petalostigma pubescens*	Mouse leukemia L1210, P388 & mouse liver cancer cells
5	 Cucurbitacins (14)	 *Solanum seaforthianum*	In vivo antitumor activity against P388, L1210 leukemia, B16 melanoma and Lewis lung tumor
6	 AMR-Me (15)	 *Amoora rohituka*	Human leukemia CEM cells
7	 Acalyphaser A (16)	 *Ansonia siamensis*	In vivo P388 leukemia

Figure 2. Structures, plant sources & activities of Terpenes.

It was derived from a triterpene acid isolated from the bark of a tropical tree *Amoora rohituka* grown wild in India. It was reported that AMR-Me inhibits telomerase activity by decreasing the hTERT expression and induced apoptosis in human lymphoblastic leukemic CEM cells [30]. Structurally derived new tetraterpene, Acalyphaser A (16) (Figure 2) exhibited no cytotoxic activity against P388 cell (ED_{50} value.100 ug/ml) but *A. siamensis* extract showed the strongest cytotoxic activity. Isoprenoid (Volatile) a broad class of mevalonate–derived phytochemicals ubiquitous in the plant kingdom, Suppress the proliferation of tumor cells and the growth of implanted tumors. Out of 179 volatile isoprenoids (constituent of fruits, vegetables and herbs) spanning seven plant families, 41 were commercially available isoprenoids for tumor suppressive potency in murine leukemia cells. They act through cell cycle arrest at the G_0-G_1 phase and induction of apoptosis [31].

Jacaranone (17) (Figure 3) possessed activity against P388 leukemia only, no activity has been found against L1210, B16 melanoma. It is isolated from *Ternstroemia japonica thumb* (Theaceae) widely distributed in Korea, Japan, Taiwan, and China [32]. Lapachol (18) (Figure 3) is originally obtained from *Stereospermum suaveolens* (Roxb.) DC., has been carried in to clinical trial on the basis of its high walker 256 activity even when given orally. Lack of toxicity permitted large oral doses but sufficiently high blood levels could not be obtained to show therapeutic effect [6]. This lead to termination of further clinical development of Lapachol [33]. Many naturally derived substituted antraquinones (morindaparvin-A and napthaquinones) possess cytotoxic antileukemic activities [34]. Beta lapachone (19) (Figure 3) has been shown to inhibit reverse transcriptase from myeloblastus virus and Rauscher murine leukemia virus [35]. Unlike Camptothecin, it does not stabilize the cleavable complex, indicating different mechanism of action in terms of topoisomerase-I inhibitor [36].

Quinones

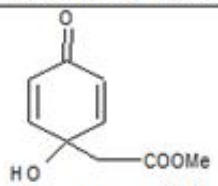
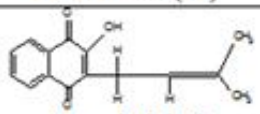
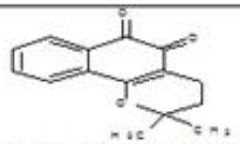
No.	Structure & Name	Sources	Activities
1	 Jacaranone (17)	 *Ternstroemia japonica thumb*	P388 leukemia
2	 Lapachol (18)	 *Stereospermum suaveolens*	Walker 256
3	 Beta lapachone (19)	 *Tabebuia impetiginosa*	P388 and L1210 leukemia

Figure 3. Structures, plant sources & activities of Quinones.

4. Sterols

The phytosterol and their plycosides are widely distributed in plants. Only daucosterol marginally showed activity in P388 leukemia. Other phytosterols such as cholesterol, ergosterol and stigmasterol have been tested in a variety of tumors, no one of them active against L1210, P388 leukemia and Walker256 sarcoma. In addition, inactivity of Stigmasterol (20) (Figure 4) was found in P388 leukemia and Ergosterol was found in KB cells [6]. Other phytosterols including Diosgenin (21) (Figure 4) and Solamargine (22) (Figure 4) [37] were potent inducers of apoptosis in K562 cell line [38]. Diosgenin, a steroid Saponin of *Trigonella foenum graecum* (Fenugreek) has been reported as inducer of apoptosis in P388 murine lymphocytic leukemia cells [39]. Solamargine, an alkaloid from Chinese herb *Solanum incanum*, has been observed to induce apoptosis via up-regulation of TNF (Tumor necrosis factor) receptor-I [40].

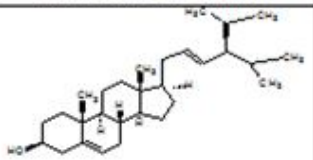
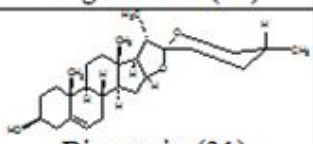
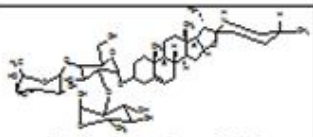
Sterols			
No.	Structure & Name	Sources	Activities
1	 Stigmasterol (20)	 *Ophiopogon japonicus*	P388 leukemia
2	 Diosgenin (21)	 *Trigonella foenum graecum*	K562 cell line
3	 Solamargine (22)	 *Brugmansia suaveolens*	P388 murine lymphocytic leukemia cells

Figure 4. Structures, plant sources & activities of Sterols.

5. Flavonoids

The Flavonoids may be divided into ten types: flavones, flavonols, flavonones, flavanone, flavanole, flavanonole, chalcones, xanthones, isoflavones and biflavones [41]. Sophoranone (23) (Figure 5), extracted from a traditional Chinese medicine *Shan dou gen* (constituent of root of *Sophora subprostrata*) [42], inhibited cell growth and induced apoptosis in various lines of cancer cells such as human stomach cancer MKN7 cells and human leukemia U937 cells [43]. Schinazi et al showed that Baicalein (24) (Figure 5) inhibited certain viruses in vitro, including the Rauscher marine leukemia virus and the HIV virus, as well as cellular DNA polymerases, and that the inhibition of reverse transcriptase by the flavone Baicalein is highly specific. These facts suggest that the flavone baicalein may be less toxic than the flavonols to the DNA and RNA polymerase in the host cell infected with retroviruses [41]. Out of the three constituents of *Scutellaria baicalensis*, Baicalein possesses highest activity against murine leukemia cell [44]. In addition, several flavonoids were tested for activity against Moloney Murine Leukemia Virus (MMLV) [45]. Isoflavones, Genistein (25) and Daidzein (26) (Figure 5), have been reported as anti-metastatic agents having activity against B16 murine melanoma cells [46]. Quercetin (27) (Figure 5) inhibited murine leukemia WEHI-3 cells in vivo and promoted immune response [47]. *Ligaria cuneifolia (R et P) tiegh*. (Loranthaceae) extracts inhibit proliferation of murine nitrogen- activated lymphocytes as well as murine T leukemia (LB) and breast tumor cells (MMT). Inhibition of proliferation was mediated by apoptosis [47]. Artoindonesianin P (28) (Figure 5), a new prenylated flavone isolated from tree bark of *Artocarpus lanceifolius*, along with three known compounds - Artobiloxanthones, Cycloartobiloxanthone and Artonol B - exhibited cytotoxic activity (IC50 5.9, 1.7, 4.6 and >100 ug/ml, respectively) against murine leukemia P388 cells [48]. Myricetin (29) (Figure 5), a naturally occurring flavonol, has shown antiviral activity against reverse transcriptase from MMLV and Rauscher murine leukemia virus. SAR study showed that free hydroxyl group of flavonoid at 3, 4' position enhanced inhibition [49, 50]. It was reported that Methyl jasmonate (30) (Figure 5) exhibits anticancer activity in vitro and vivo. Methyl jasmonate induces suppression of cellular proliferation and death in human and mouse cancer cell lines. Thus, Methyl jasmonate was considered as a novel lead compound for cancer treatment [51]. Studies on drug target delivery system have shown that Methyl jasmonate binds to mitochondrial hexokinase, so that ultimately it dissociates

from the mitochondria-VDAC interaction with release of cytochrome C. This effect of Methyl jasmonate has been validated in mitochondrial fraction from murine B16 carcinoma cell line [52].

Flavonoids

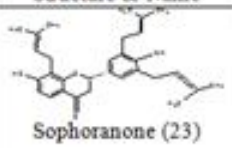
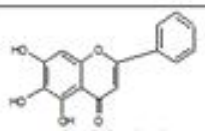
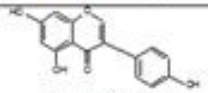
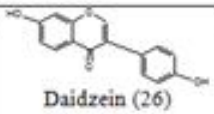
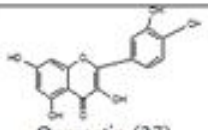
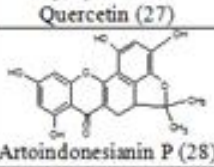
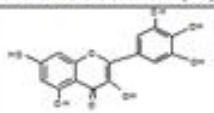
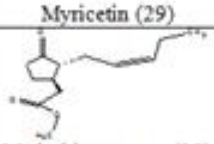
No.	Structure & Name	Sources	Activities
1	 Sophoranone (23)	 *Sophora subprostrata*	Human stomach cancer MKN7 cells and human leukemia U937 cells
2	 Baicalein (24)	 *Scutellaria baicalensis*	Rauscher marine leukemia virus and the HIV virus
3	 Genistein (25)	 *Lupinus perennis*	B16 murine melanoma cells
4	 Daidzein (26)	 *Pueraria lobata*	B16 murine melanoma cells
5	 Quercetin (27)	 *Lingaria cuneifolia*	In vivo WEHI-3 cells
6	 Artoindonesianin P (28)	 *Artocarpus lanceifolius*	P388 leukemia cells
7	 Myricetin (29)	 *Vitis vinifera sativa*	P388 and L1210 leukemia
8	 Methyl jasmonate (30)	 *Jasminum sambac*	Murine B16 carcinoma cell line

Figure 5. Structures, plant sources & activities of Flavonoids.

6. Lignans

They are found in some plants with activity against KB cells [6]. Podophyllotoxin (31) (Figure 6) was evaluated in vitro to establish its cytotoxicity against cell cultures of P-388 murine leukaemia, A549 lung carcinoma [53-56]. It is the most abundant lignan isolated from podophyllin resin obtained from species of the genera *Podophyllum* (Berberidaceae) [57].

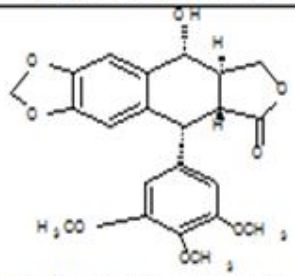
Lignan			
No.	Structure & Name	Source	Activity
1	 Podophyllotoxin (31)	 *Podophyllum peltatum*	P388 murine leukemia, A549 lung carcinoma

Figure 6. Structure, plant source & activity of Podophyllotoxin.

7. Saponins

This widely disseminated class of plant constituents generally possesses activity against Walker 256 and sarcoma 180, but lacks activity in KB cells. Mixture of saponins has also been reported on a mixture of monodesmoside saponins, which were not active as pure compounds, to be highly cytotoxic against P388 and colon cell lines [58] (ED_{50} Values of 2.3 and 3.6 ug/ml) [59, 60]. Alpha-Hederin (32) (Figure 7) may act through induction of apoptosis, since in murine leukemia P388 cells [61-63]. Deglycosylated Saponin such as ginsenosides (32a) was obtained from red *ginseng*, induced P388 murine (in vivo) leukemia cells [64].

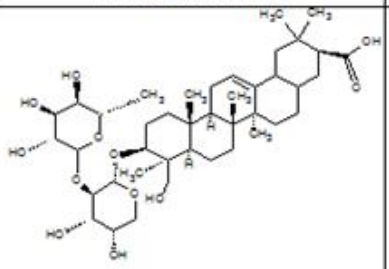
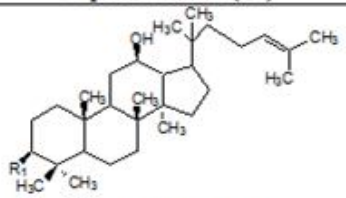
Saponin			
No.	Structure & Name	Sources	Activities
1	 alpha-Hederin (32)	 *Nigella sativa*	P388 leukemia cells
2	 R_1= 0-gly (2-1) gly Ginsenoside (32a)	 *Panax ginseng*	P388 leukemia cells (in vivo)

Figure 7. Structure, plant source & activity of alpha-Hederin.

8. Quassinoids (Simaroubolides)

Bruceantin (33) (Figure 8) was isolated from *Brucea antidysenteria J. F. Mill*, a plant used in Ethiopia and Eritrea for cancer. Halocanthone (34) (Figure 8), from *Halocanthamoryi gray*, is cytotoxic, a large proportion is highly active in P388 leukemia and several are also active in L1210 leukemia or B16 melanoma. Chaparrinone (35) (Figure 8) and

its analogue have been incubated with murine leukemia cells. A moderate activity was found. While 14-hydroxy Chaparrinone had high activity against P388 cells [65].

Quassinoids (Simaroubolides)

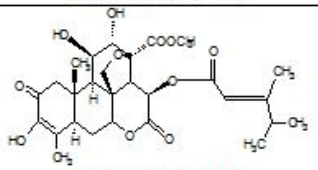
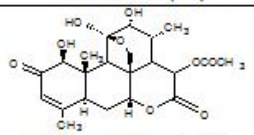
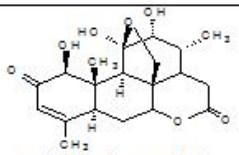
No.	Structure & Name	Sources	Activities
1	 Bruceantin (33)	 *Brucea antidysenteria mill*	P388 cells
2	 Halocanthone (34)	 *Celastrus orbiculatus*	P388 leukemia and several are also active in L1210 leukemia or B16 melanoma
3	 Chaparrinone (35)	 *Ailanthus altissima*	P388 cells

Figure 8. Structures, plant sources & activities of Quassinoids (Simaroubolides).

9. Ansa Macrolides

The large macrocyclic lactone ring, frequently N-heterocyclic, incorporating within it an m or p-bridge aromatic moiety. Maytansine (36) (Figure 9) was isolated from several *Maytenus* species. The group is generally cytotoxic and is unusually active in P388 leukemia at remarkably low doses. Maytansine, the most readily available member of the group, is also active in L1210 leukemia and B16 melanoma is now in clinical trial [6].

Ansa macrolide

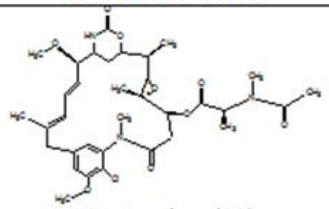
No.	Structure & Name	Sources	Activities
1	 Maytansine (36)	 *Maytenus boaria*	L1210 leukemia and B16 melanoma

Figure 9. Structure, plant source & activity of Maytansine.

10. Antrapyrazoles

Chromophore modification of the Antracenediones (37) (Figure 10) related to mitoxantrone, in an attempt to provide agents with diminished or no cardiotoxicity has resulted in a novel class of DNA binders. A ring of 7,10-dihydroxyantrapyrazoles were derived from amine condensation with intermediate 5-chloro 7,10-dihydroxyantrapyrazoles. Potent in vitro activity was demonstrated against murine L1210 leukemia in vitro (IC_{50}=10^{-7}-10^{-8}M) as well as against P388 leukemia in vivo over a wide range of structural variants [66].

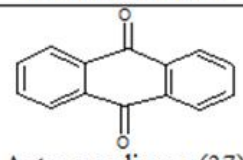
Antracenediones			
No.	Structure & Name	Sources	Activities
1	 Antracenediones (37)	 *Rheum rhabarbarum*	L1210 leukemia in vitro as well as against P388 leukemia

Figure 10. Structure, plant source & activity of Antracenediones.

11. Essential Oils

Anti-proliferative activity of 17 essential oils from Thai medicinal plants was studied [67]. Several other essential oils, such as *Ocimum sanctum*, *Citrus citrates*, *Citrate citrates, Alpinia officinarum*, *Lavndila angustifolia, Vetiveria zizanioides, Zingiber montanum, Piper nigram, Crmbopogon nardus, Curcuma longa, Ocimum basilicum, Citrus hystrix, Piper betle, Albizia lebbeck, Ocimum americanum, Mentha spicata* and *Psidium guajava* have shown an inhibition of the proliferation of murine leukemia [68]. Essential oil extracted from leaves of *Psidium guajava* was highly effective against KB and murine leukemia P388 cells [69].

12. Miscellaneous

Artemisinin (38) (Figure 11): Accumulation of P388 and A549 cells in the G1 Phase due to the presence of cyano and aryl group in artimisinin derivatives [70]. L-Canavanine (39) (Figure 11) is non-protein toxic amino acid (2-amino-4-guanidinooxy-butyric acid) (Cav). Cav is an analogue of L-arginine, naturally abundant in the seed of *C. ensiformis*, *C. gladiate* and *C. canthartica*. It showed activity against Walker carcinoma, human melanoma, and murine L1210 leukemia (in vivo) [71]. Quassinoid glucoside Bruceantinoside-A & B (40, 41) (Figure 11) [72] and bruceanic acids isolated after testing their activity against tumor. During preliminary test, these compounds were found effective against KB and murine lymphomatic leukemia P388 [73]. *Betula platyphylla var japonica* extract prevented carcinogenesis in murine model through induction of apoptosis. Extract increase the expression of the pro-apoptotic Bax (BCl_2 including X) protein and lead to activation of caspase-3 and cleavage of PARP [74]. Matrixmetalloproteinase-2 has been inhibited by Curcumin upon treatment with highly metastatic murine melanoma cells B16F10. It has been evaluated that the cytotoxic effect of ar-turmerone on the K56, L1210, U937 and RBL-$2H_3$ cell lines using MTT assay [75, 76]. Curcumin (42) and ar-turmerone (43) (Figure 11) are components of turmeric. Curcumin, the main yellow bioactive component, has been reported with various medicinal properties [76]. Mistletoe's Lectins from *Viscum album* L. are cytotoxic glycoproteins having approximately 10,000 molecular weight, used to detect apoptotic murine leukemia L1210 cells [77, 78].

13. Conclusion

Nature continues to be the most prolific source of biologically active and diverse chemotypes. Although relatively few of the actual isolated compounds advance to become clinically effective drugs in their own right, these unique molecules often serve as models for the preparation of analogues using chemical methodology such as total or combinatorial synthesis, or manipulation of biosynthetic pathways [16]**.** Herein, we reviewed some plant derived active compounds having activity against murine leukemia cells, which will be used in future for the development of active components against human leukemia, breast cancer, colon cancer, and lung cancer, without adverse effects.

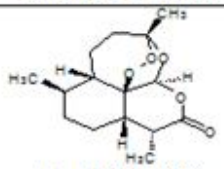
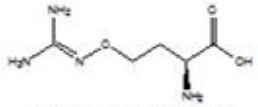
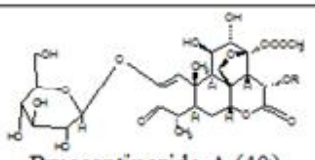
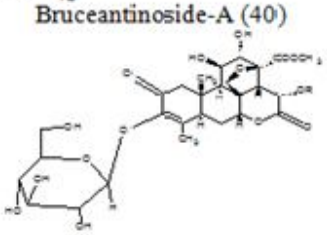
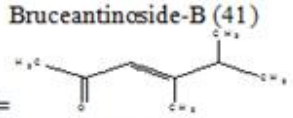
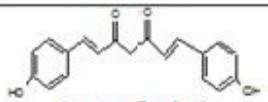
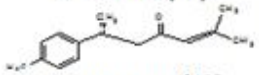
Miscellaneous			
No.	Structure & Name	Sources	Activities
1	 Artemisinin (38)	 *Artemisia annua*	P388 and A549 cells
2	 L-Canavanine (39)	 *Glycine max*	Walker carcinoma, human melanoma, and murine L1210 leukemia (in vivo)
3	 Bruceantinoside-A (40)  Bruceantinoside-B (41)  R=	 *Betula platyphylla var japonica*	KB and murine lymphomatic leukemia P388
4	 Curcumin (42)  ar-turmerone (43)	 *Curcuma longa*	K56, L1210, U937 and RBL-2H3 cell

Figure 11. Structures plant sources & activities of Miscellaneous compounds.

Abbreviations

L1210 & P388, murine leukemia cell lines; MuLV, Murine leukemia virus; KB, carcinoma cell; walker 256, tumor cell; DNA, Deoxyribonucleic acid; HL-60, Human leukemia; WEHI-3, myelomonocytic leukemia; SAR, Structure activity relationship; AMR-Me, Methyl-25-hydroxy-3-oxoolean-12-en-28 oate; hTERT, Human telomerase reverse transcriptase; CEM, Human lymphoblastic leukemia cell; B16, melanoma cell; HEL, Human erythroleukemia cell; K562, Human immortalised myelogenous leukemia line; TNF, Tumor necrosis factor; MKN7, Human stomach cancer cell; HIV, Human immunodeficiency virus; RNA, Ribonucleic acid; MMLV, Moloney murine leukemia virus; VDAC, voltage-dependent anion channel; LB, Nonimmunogenic T cell; MMT, Murine T leukemia; Breast tumor cell; A549, Lung carcinoma cell; PARP, Poly adenosine diphosphate-ribose polymerase; B16F10, Metastatic murine melanoma cells; BCl2, B-cell lymphoma; MTT assay, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

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