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Bisbenzylisoquinoline Alkaloids From Genus Triclisia As Potential Anticancer Agents: A Review

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Abstract
Despite advancements in anticancer strategies such as radiotherapy, surgery, chemotherapy, and immunotherapy, cancer continues to be a global health burden. There were an estimated 20 million new cancer cases and 9.7 million deaths in 2022 with lung cancer leading in incidence and mortality. It ranks as the second most prevalent cause of death globally. Some of the challenges encountered in cancer treatment and management include toxicity of conventional treatments and multidrug resistance among others. There is therefore need for continued search for new drugs to counter these challenges and lessen the cancer burden. Plants are a potential source of compounds that can be developed into new anticancer agents. Bisbenylisoquinoline (BBIQ) alkaloids from plants belonging to the family Menispermaceae are a good example of compounds that have been shown to possess anticancer activity. The genus Triclisia belongs to this family. The plants in this genus have found use in traditional medicine where they are used in the management and treatment of many conditions and ailments including cancer. The main purpose of this review is to highlight the anticancer potential of BBIQ alkaloids from plants in this genus. Information was collected from scientific databases and relevant books. A literature survey revealed that there are five species in the genus Triclisia from which a total of 24 BBIQ alkaloids have been isolated. These are: Triclisia patens Oliv, T. dictyophylla Diels, T. gilletii DeWild, T. subcordata Oliv. and T. sacleuxii (Pierre) Diels. Phaeanthine, 1,2-dehydroapateline, tetrandrine, cycleanine, fangchinoline, aromoline, pycmanilline and cocsuline are some of the BBIQ alkaloids from these plants that are reported to possess anticancer properties. Some of the compounds like tetrandrine and fangchinoline have been extensively studied while others remain unexplored. The BBIQ alkaloids that have shown promising activity in vitro and in vivo should be subjected to preclinical trials and possibly clinical trials to assess their safety and effectiveness. Combination therapy and structural modifications are also areas that need more focus. The unexplored alkaloids should be studied to discover their anticancer potential. All these will help reduce the relatively high morbidity and mortality associated with cancer globally.
Keywords: *Menispermaceae, Triclisia, bisbenzylisoquinoline alkaloids, cancer, cytotoxicity.*

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I. Introduction

Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs; the latter process is referred to as metastasis. Widespread metastases are the primary cause of death from cancer[1]. Despite advancements in anticancer strategies such as radiotherapy, surgery, chemotherapy, and immunotherapy, cancer continues to be a global health burden. According to International Agency for Research on Cancer (IARC), an agency of the WHO, there were an estimated 20 million new cancer cases and 9.7 million deaths in 2022 with lung cancer leading in incidence and mortality[2]. Cancer ranks as the second most prevalent cause of death globally[3]. The global cancer burden is not evenly distributed. There is a clear correlation between socioeconomic development and cancer rates with poor countries bearing the greatest burden. This is due to factors such as lack of proper preventive measures, late diagnosis and high treatment costs. Asia leads in incidence, mortality and prevalence. Over 35 million new cancer cases are predicted in 2050, a 77% increase from the estimated 20 million cases in 2022[2]. Challenges that continue to be encountered in cancer management and treatment globally include; multi-drug resistance (MDR), immune-related side effects, high costs, immunosuppressive tumour microenvironments and toxicity of conventional treatments[4,5,6].

Till 2019, approximately 84% of the anticancer drugs in clinical use were either of purely natural origin or with natural pharmacophore, semi-synthetically modified, or the ones that mimic the natural products or the botanical formulations[7,8]. Bisbenzylisoquinoline (BBIQ) alkaloids are among the compounds that have been shown to possess anticancer properties with some of them in clinical use as anticancer agents. They have shown great promise in combating some of the challenges in cancer treatment like MDR and toxicity of

conventional treatments. This review highlights the anticancer potential of BBIQ alkaloids from plants in the genus Triclisia. It identifies the gaps and points out areas of further research that will enable full exploitation of the anticancer potential of these alkaloids. These alkaloids are a defining feature of the family Menispermaceae, they are abundant and display a wide variety of pharmacological activities. Triclisia is a genus in this family from which BBIQ alkaloids have been isolated.

II. Materials And Methods

Information on plants in the genus Triclisa, their constituent BBIQ alkaloids and their cytotoxic activities was collected from the scientific search engines: Web of science, Google Scholar, SciFinder, and PubMed. Relevant books were also used. The chemical structures of BBIQ alkaloids isolated from plants in the genus Triclisia were drawn using ChemDraw Professional 15.0 software.

III. Results And Discussion

The Genus Triclisia

There are about 20 species of the genus Triclisia known throughout globe with 12 in tropical Africa Region[9]. This review identified 5 Triclisia species from which compounds have been isolated. These are *Triclisia dictyophylla* Diels, *Triclisia patens* Oliv., *Triclisia gilletii* (DeWild), *Triclisia subcordata* Oliv. and *Triclisia sacleuxii* (Pierre) Diels. Various parts of all these plants have found use as sources of medicine for the treatment of various ailments in traditional medicine.

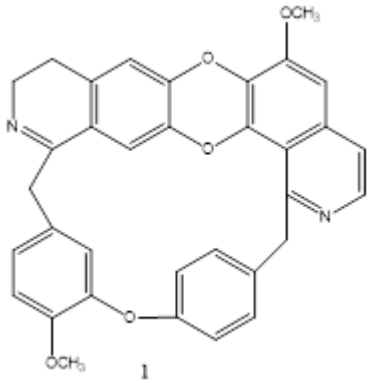
Bisbenzylisoquinoline (BBIQ) Alkaloids

BBIQ alkaloids are built up of two benzylisoquinoline (BI) units linked by ether bridges. In addition to this ether linkage, methylenoxy bridging or direct carbon-carbon bonding is also found between the two BI units. A variety of structural patterns arise in the BBIQ molecules due to differences in the number of aromatic oxygen substituents present, the number of ether linkages, the nature of ether bridges, viz., diphenyl ether or benzylphenyl ether and the sites on the two BI units at which the ether or the carbon-carbon bond originates[10]. Based on these differences, the BBIQ alkaloids are classified into groups and subgroups[10, 11].

There are about 500 natural products belonging to this large alkaloid class[11]. The number is likely higher than this considering that this figure was given about six years ago. These alkaloids mostly occur in the Menispermaceae, Berberidaceae, Lauraceae, and Ranunculaceae plant families, which preferably grow in tropical and subtropical regions[12-16]. A good number of plants from these families have been used in traditional medicine to treat and manage various ailments and conditions[17-20]. Formulations containing parts of these plants have also been used for centuries as an arrow poison in South America[21]. Most of these traditional uses can be attributed partly to the presence of BBIQ alkaloids in various parts of these plants. This is supported by reports on the pharmacological activities of these alkaloids isolated from numerous plants in these families. There are five species in the genus Triclisia from which a total of 24 BBIQ alkaloids have been isolated. These are: *Triclisia. sacleuxii* (Pierre) Diels*, T. subcordata* Oliv., *T. gilletii* DeWild, *T. patens* Oliv. and *T. dictyophylla* Diels.

***T. sacleuxii* (Pierre)** Diels

T. sacleuxii is a climbing plant producing stems 10 - 15 metres long[21]. It is found in Angola, Central African Republic, Congo, Gabon, Kenya, Mozambique and Tanzania[22]. BBIQ alkaloids have been isolated from the roots and leaves of this plant. From the roots gasabiimine (**1**), phaeanthine (**2**), 1,2-dehydroapateline (**3**), N-methylapateline (**4**), 1,2-dehydrotelobine (**5**) and *O*- methylcocsoline (**6**) have been isolated[23-25]. Lindoldhamine (**7**)[25] and isotetrandrine (**8**) have been isolated from the leaves[26].



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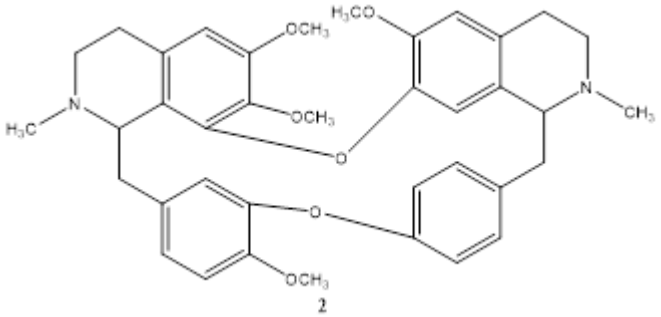

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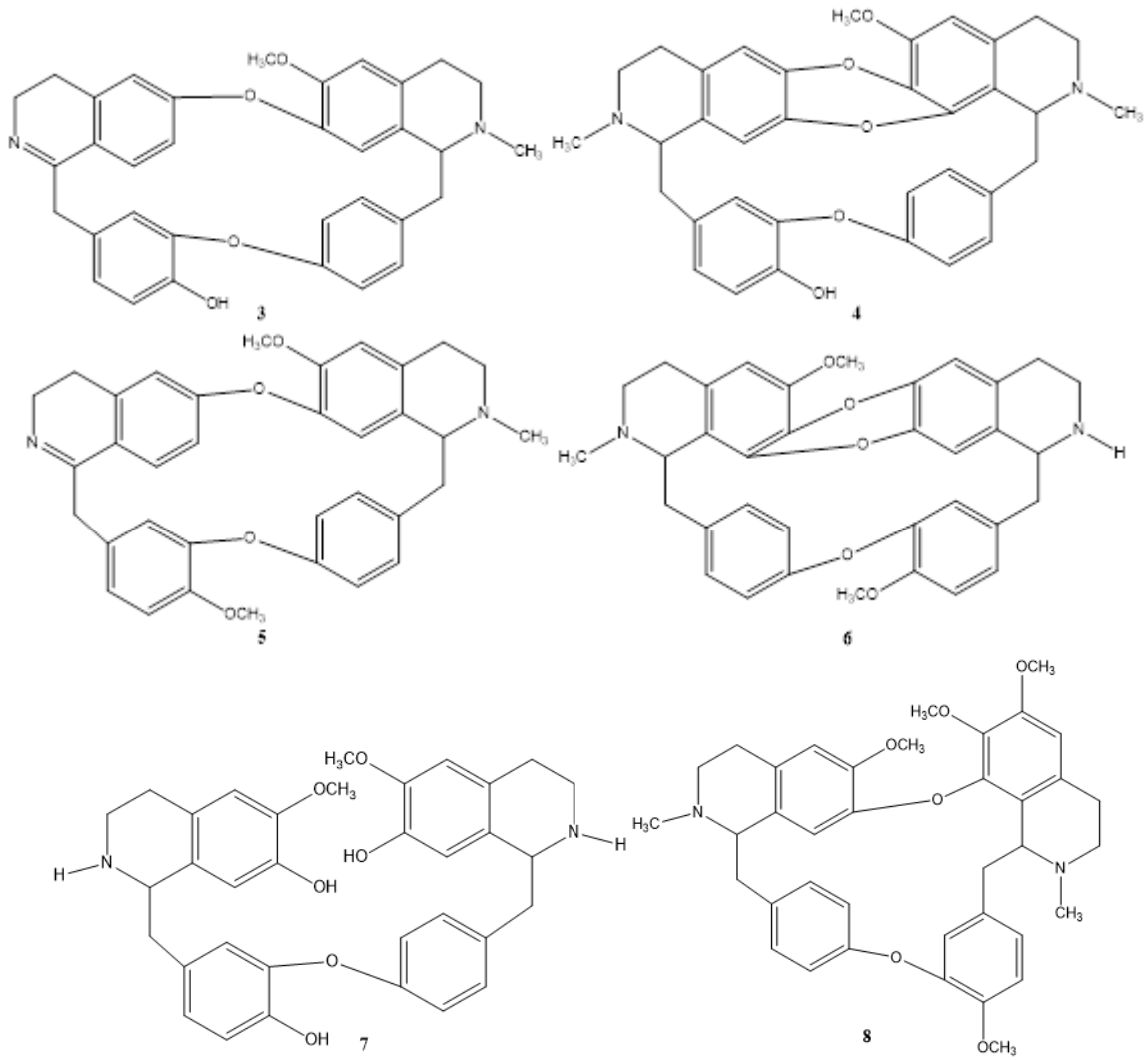
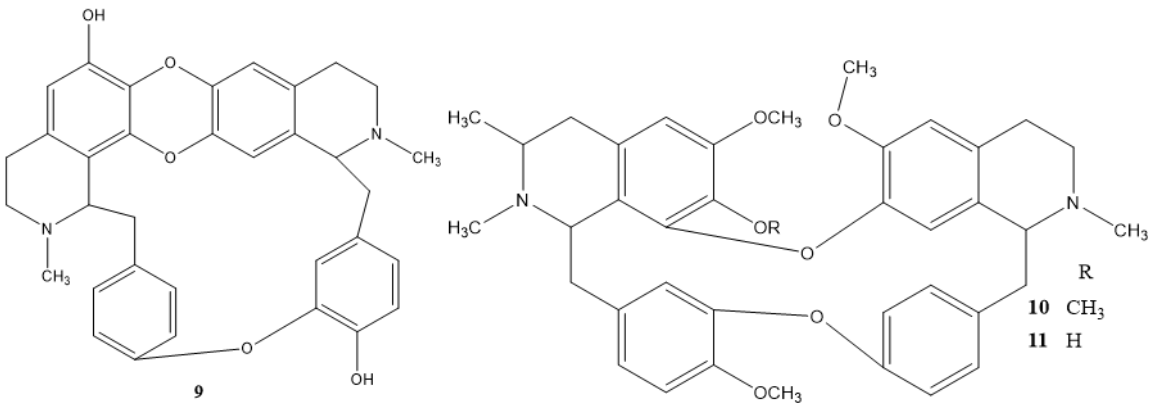


Fig. 1: Chemical structures of BBIQ alkaloids from *T. sacleuxii* (Pierre) Diels: Gasabiimine (**1**), phaeanthine (**2**), 1,2-dehydroapateline (**3**), N-methylapateline (**4**), 1,2-dehydrotelobine (**5**) and *O*- methylcocsoline (**6**), lindoldhamine (**7**) and isotetrandrine (**8**)

***T. subcordata* Oliv.**

This is a slender woody twiner with brownish stems 6–15 ft. long. It has green flowers which later turn brown. Its fruits are orange[27]. It is found in Benin, Burkina Faso, Ghana, Ivory Coast, Nigeria and Togo[28].

Early phytochemical studies in the 1970s revealed the presence of only three BBIQ alkaloids: tricordatine (**9**)[29], fangchinoline (**10**)[30] and tetrandrine (**11**)[31] from this plant species. Additional BBIQ alkaloids from the roots have since been reported. These include cycleanine (**12**)[32], isochondodendrine (**13**) and 2'-norcocsuline (**14**)[33].



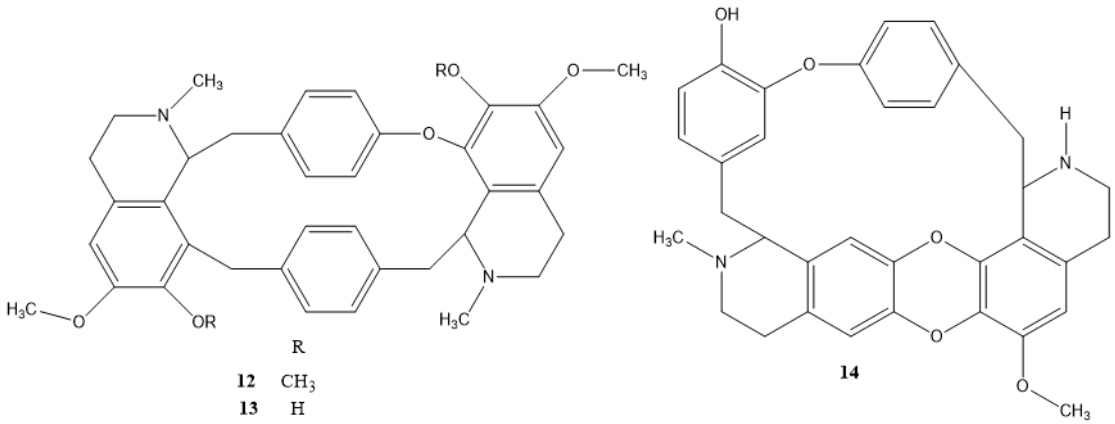
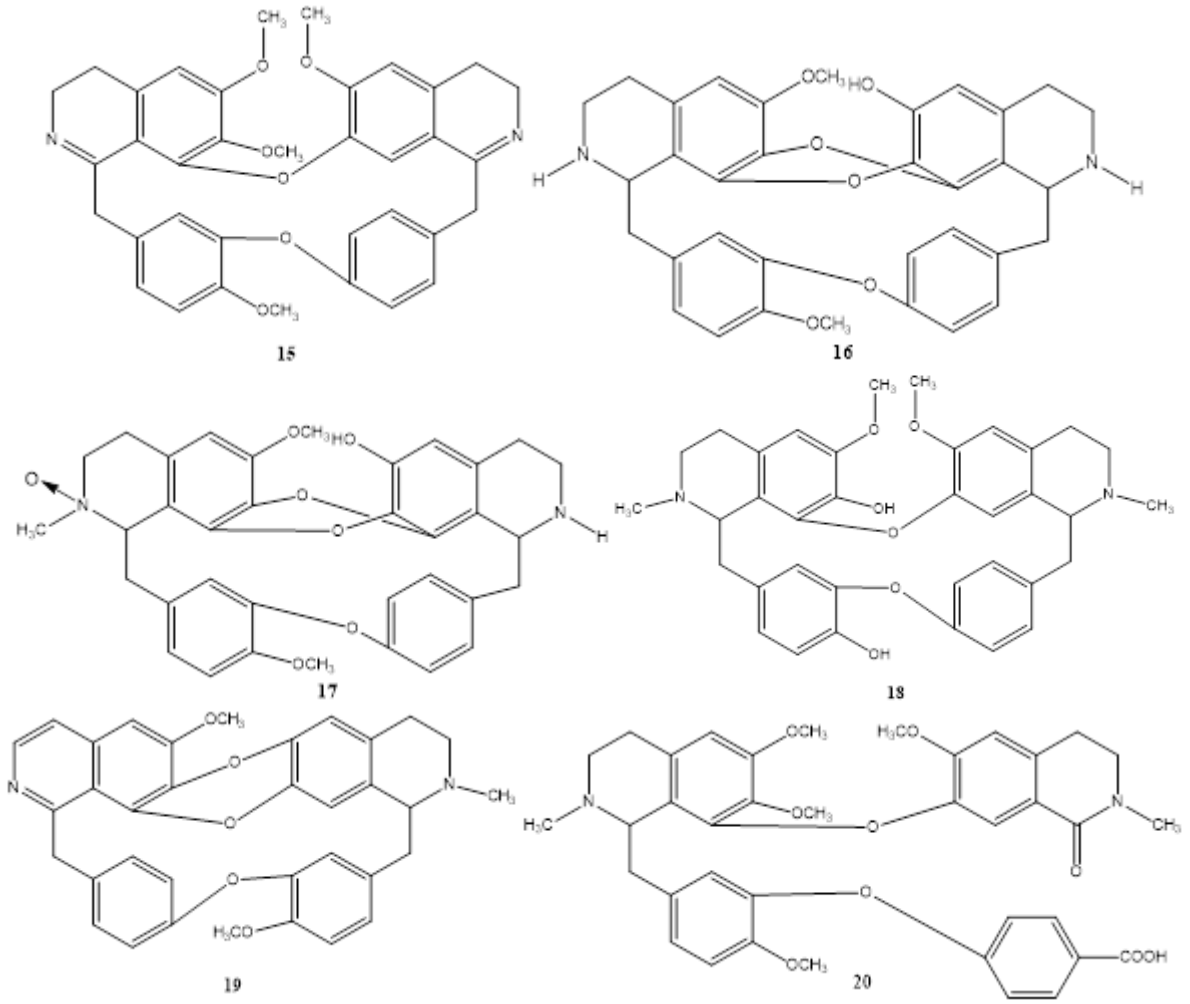


Fig. 2: Chemical structures of BBIQ alkaloids from *T. subcordata* Oliv.: Tricordatine (**9**), fangchinoline (**10**), tetrandrine (**11**), cycleanine (**12**), isochondodendrine (**13**) and 2'- norcocsuline (**14**).

***T. gilletii* DeWild**

T. gilletii De Wild is a robust creeper of up to 10 cm diameter, of the lowland dense rain-forest occurring from Liberia to Angola[34].

Several BBIQ alkaloids have been isolated from different parts (leaves, stem and roots) of this plant. Stebisimine (**15**)[30,35], gilletine (**16**)[36], isogilletine-N-oxide (**17**) and obamegine (**18**)[35] have been isolated from the leaves. Isotetrandrine (**8**), trigilletimine (**19**)[36], pycmanilline (**20**), phaeanthine (**2**)[37] and cocsuline (**21**)[29,30] are reported from the stem. The following have been isolated from the roots; isotetrandrine (**8**)[30], trigilletimine (**19**)[31], trigilletine (**22**) and tricordatine (**9**)[29].



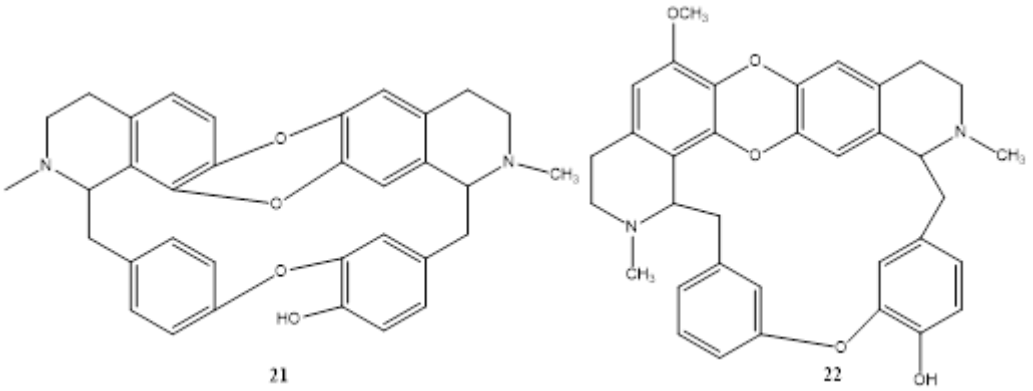


Fig. 3: Chemical structures of stebisimine (**15**), gilletine (**16**), isogilletine-N-oxide (**17**), obamegine (**18**), trigilletimine (**19**, pycmanilline (**20**), cocsuline (**21**) and trigilletine (**22**)

***T. patens* Oliv.**

T. patens Oliv., is a dioecious liana with a stem up to 6 cm in diameter and a length of up to 12 m. The leaves alternate, are whole, and have pinnate veins. The fruit is made up of spheroid, flattened drupes and the flowers are unisex[38]. It is a native of Burkina Faso, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Senegal and Sierra Leone[39].

Phaeanthine (**2**), trigilletimine (**19**), pycnamine (**20**), cocsuline (**21**), aromoline (**23**) and *N*,*N*'-dimethylphaeanthine (**24**) have been isolated from its leaves[30,38,40,41]. From the stem, phaeanthine (**2**) and trigilletimine (**19**) have been isolated[31,42]. Trigilletimine (**19**) has also been isolated from the roots[31].

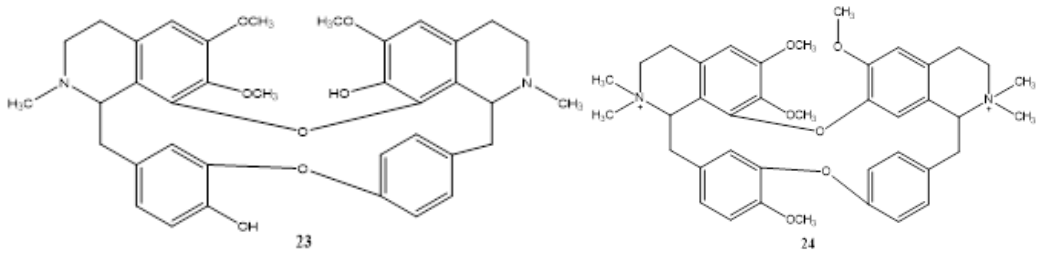


Fig. 4: Chemical structures of aromoline (**23**) and *N*,*N*'- dimethylphaeanthine (**24**)

***T. dictyophylla* Diels**

T. dictyophylla Diels is a climbing plant or scrambling shrub of the lowland dense rain forest with stems that can be up to 30 m long. The plant occurs from Liberia to Central Africa, Democratic Republic of Congo, Angola and Tanzania[34]. Phaeanthine (**2**), *N*,*N*' – dimethylphaeanthine (**24**), trigilletimine (**19**) and cocsuline (**21**) and have been isolated from the whole plant[20,41,43].

Cytotoxic BBIQs from Triclisia Species

Most of the BBIQ alkaloids isolated from plants in the genus Triclisia have been reported to possess cytotoxic activity hence they have anticancer potential. Some of the alkaloids like phaeanthine (**2**), isotetrandrine (**8**), fangchinoline (**10**), tetrandrine (**11**), cycleanine (**12**) and isochondodendrine (**13**) have been extensively studied. Others have been studied to a small extent while some remain unexplored.

Phaeanthine (2)

This BBIQ alkaloid has potential as an anticancer agent against different cancers according to various studies. For example, it has been observed to suppress the growth of cervical cancer (HeLa) cells with an IC_{50} value of 8.11 μM[44]. Its mechanism of action involves the activation of the intrinsic mitochondrial pathway; ultimately leading to apoptosis. It has also been observed that **2** induces several molecular changes. It reduces the levels of mitogen-activated protein kinase (Mcl-1) while simultaneously increasing B-cell lymphoma 2 (Bcl-2) associated X protein (BAX) and Bcl-2 homology domain (BH3) interacting domain death agonist (BID) expression. Furthermore, it elevates the cytoplasmic concentration of cytochrome c and leads to the activation of cleaved caspases 9 and 3[44]. These are executioner caspases which play central roles in inducing apoptosis[45]. **2** is also reported to possess cytotoxic activity against human lung fibroblasts, MCR-5 cells[24,37] and KB (carcinoma of the human nasopharynx) cells[46,47].

Isotetrandrine (**8**)

The earliest report on the anticancer potential of this alkaloid was reported in 1976[48]. Their study revealed that **8** has cytotoxic effects *in vitro* and antitumour effects *in vivo*. It was cytotoxic against cultured HeLa and HeLa-S_3 cells with ED_{50} values of 5.8 and 10 μg/ml respectively. It had antitumour effects against both ascites type and solid type tumours in mice. This alkaloid also has cytotoxic effects against human oral epidermoid carcinoma (KB) cells with ED_{50} value of 10600 nM[46]. In addition, results from a study on P-glycoprotein-mediated multidrug resistance in human breast cancer doxorubicin-resistant (MCF-7/DOX) cells suggest that it might become a candidate of effective MDR reversing agent in cancer chemotherapy[49].

Fangchinoline (**10**)

Various reports reveal that this alkaloid inhibits the proliferation of different types of cancer cells. For example, it inhibits the proliferation of MDA-MB-231 and MCF-7 breast cancer cells, with IC_{50} values of 25.2 and 34.6 μmol/L, respectively[50]. In another study by Liu *et al*.[51], it was cytotoxic against MDA-MB-231 cells with IC_{50} value of 12.3 μmol/L, comparable to that of vincristine (13.1 μmol/L). The antiproliferation effect of **10** towards MDA-MB-231 cells is also reported by Wang *et al*.[52], where its IC_{50} values at 24 and 48 h were 14.3 and 10.5 lg/mL, respectively. Flow cytometry showed that MDA-MB-231 cell death was 16.4% and 28.0% after 24 and 48 h treatment with 20 μg/mL of **10**, respectively.

A study by Bao *et al*.[53] revealed that **10** significantly inhibits the growth of conjunctival melanoma (CM) cells *in vitro* and *in vivo*. This is a rare and fatal ocular tumour with poor prognosis. In this study, it exhibited *in vitro* anti-proliferative activity against four CM cell lines: CM-A516, CRMM1, CRMM2 and CM2005.1 with IC_{50} values of 5.67, 2.68, 3.60 and 7.40 μM respectively. It also exhibited *in vivo* antitumour effects where the tumour volume of the treated group (at a dose of 50mg/Kg/day), was less by 27% compared to the control group. In addition, it increased the *in vivo* antitumour efficacy of cisplatin and reduced its dosage and toxicity. Mechanistic experiments in this study indicated that **10** suppressed the homologous recombination (HR)-directed DNA repair by binding with far upstream element binding protein 2 (FUBP2) and downregulating the expression of HR factors BRCA1 and RAD51.

In a study by Guo *et al*.[54], **10** effectively suppressed proliferation and invasion of A549 lung cancer cell line by inhibiting the phosphorylation of focal adhesion kinase (FAK) at Tyr397 position and its downstream pathways. Furthermore, it has antiproliferation activity against multiple myeloma[55], bladder cancer cells, T24 and 5637[56], hepatocellular carcinoma cells (HepG2 and PLC/ PRF/5 cells)[57], leukemia[58,59], gastric cancer[60], glioblastoma[61], pancreatic cancer[62] and prostate cancer cells[63]. The molecular mechanisms of **10** against these cancers have been widely studied. It has been observed that it inhibits cancer proliferation by interfering with migration and angiogenesis, primarily through the downregulation of mesenchymal marker proteins such as fibronectin, vimentin, Snail, and Twist[64].

Tetrandrine (**11**)

This is one of the most studied BBIQ alkaloid from Triclisia species. There are numerous reports on its anticancer activity both *in vitro* and *in vivo* against a wide range of cancers of the breast, liver, pancrease, blood (leukemia), colon, lung, bladder, cervix, prostate, ovaries, etc[33,65-70]. It is has also been used in clinical trials in combination with the conventional drugs gemcitabine and cisplatin to treat lung cancer without any side effects[71,72]. Many experiments have demonstrated that **11** has a number of anti-tumor mechanisms. It can inhibit the growth of tumor cells by inducing apoptosis, sensitizing radiotherapy, and protecting against potentially lethal injury caused by radiation. It can also alleviate radiation damage by inhibiting inflammatory reactions[71]. It has been used clinically in China for the treatment of lung cancer and leukemia[73].

Cycleanine (**12**)

In a study by Uche *et al*.[33], this alkaloid has anticancer activity on four ovarian cancer cell lines (Ovcar-8, A2780, Igrov-1, and Ovcar-4) with IC_{50} values of 1.0, 7.6, 14 and 7.2 μM respectively. It causes apoptosis as shown by activation of caspases 3/7 and cleavage of poly (ADP-ribose) polymerase to form poly (ADP-ribose) polymerase-1 by using western blot analysis. Uche *et al*.[74] also reports the cytotoxic activity of **12** against the A2780 ovarian cancer cell line with IC_{50} of 7.56 μM in and 44% viability at dose of 10μM. In addition, **12** has cytotoxic effect against human oral epidermoid carcinoma (KB) cells[46], human colon carcinoma (HCT-116) cells[75], HeLa cells[44,48], KB cells, SiHa cells and A549 cells[76] and Vero cells[77].

Isochondodendrine (**13**)

This BBIQ alkaloid is reported to possess weak to very good cytotoxic activity by a number of studies. In a study by Marshall *et al*.[47], it exhibited a very weak cytotoxic activity against KB (carcinoma of the human nasopharynx) cells with IC_{50} value >421 μM. It has moderate cytotoxic activity against human colon carcinoma (HCT-116) cells with CC_{50} values of 29 μM[75]. Despite this very weak and moderate cytotoxicity, this alkaloid

has shown similar potency to the clinically used drug carboplatin against ovarian cancer *in vitro*[32]. When assayed against four ovarian cancer cell lines (Ovcar-8, A2780, Igrov-1, and Ovcar-4) it displayed very high potency with IC_{50} values of 8.0, 3.5, 9.0 and 17 µM respectively. It acted by inducing apoptosis in ovarian cancer cells by activating caspases 3/7 amongst other mechanisms.

Other bisbenzylisoquinoline alkaloids from Triclisia species with cytotoxic activity

There are some BBIQ alkaloids from Triclisia species that are reported to have cytotoxic activity against one or two cancer cell lines only. This is a category that requires more focus. These include **3**, **4** and **5**, which possess cytotoxic activity against human fetal lung fibroblasts, MCR-5 cells with IC_{50} values of 3.61, 1.25 and 3.59 µM respectively[24].

Other BBIQ alkaloids that require more studies include **9**, **14**, **18**, **21** and **23**. They have cytotoxic effects against human oral epidermoid carcinoma (KB) cells[46]. In addition to cytotoxicity against human oral epidermoid carcinoma (KB) cells, **14**, **18**, **21** and **23** have been shown to exhibit activity against other cancer cell lines. For example, according to a study by Uche *et al*.[32], **14** possesses anticancer activity on four ovarian cancer cell lines (Ovcar-8, A2780, Igrov-1, and Ovcar-4) with IC_{50} values 1.9, 2.9, 0.8 and 6.2 µM respectively. It was found to be more potent than carboplatin in all four cancer cell lines and was observed to act by inducing apoptosis in the ovarian cancer cells. **16**, **18**, **19**, **20**, **21** and **23** possess cytotoxic activity against KB (carcinoma of the human nasopharynx) cells[47]. The cytotoxicity of **20** is further confirmed in a study by Kanyanga *et al*.[37] where it is reported to be cytotoxic against MRC-5 cells (human lung fibroblasts).

IV. Conclusion

Plants in the genus Triclisia are a rich source of BBIQ alkaloids with anticancer properties. Some of these alkaloids like **2**, **8**, **10**, **11**, **12** and **13** have been extensively studied and their mechanisms of action established while others remain unexplored. Studies have shown that some of these alkaloids like **10** and **13** have efficacies that are comparable to conventional drugs against some cancers while others like **8** are potential candidates as multidrug resistance reversing agents in cancer chemotherapy by employing combination therapy. In addition, some of them reduce toxicity and increase the efficacy of anticancer drugs in clinical use. However, there are challenges that have been observed with these alkaloids. For example, **11**, which is in clinical use, has low bioavailability.

It is also worth noting that **14** which has not been so widely studied has been shown to be more potent than a clinically used drug against ovarian cancer. This means that it may be useful as a starting point in the development of new drugs against ovarian cancer. Future research should focus on structural modifications to improve the potency of these alkaloids. There is also need for more comprehensive studies on less explored and unexplored alkaloids to uncover their full therapeutic potential. Studies to solve the challenge of bioavailability should be carried out. In addition, extensive preclinical and clinical trials of BBIQ alkaloids like **10** are necessary.

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