Flavonoid and Stilbene Cytotoxic Phytochemicals Isolated from Genus Macaranga for the Treatment of Cancer Cells: A Review

Abstract

Genus Macaranga contains more than 308 species and different species from this genus have a variety class of secondary metabolites that are used for different therapeutic purposes. Flavonoids and stilbenes are the major compounds that are isolated from different species of Macaranga. These compounds are cytotoxic to different cancer cell lines like human breast adenocarcinoma (MCF-7), human Hepatocellular (HepG2), human Cervical Carcinoma (Hela) and mouse leukemia (P388) cell lines with high to low cytotoxic activities. Schweifurthins are some stilbenes that are isolated from various Macaranga species and have different cytotoxic activity to ward many cancer cells. The synthetic analogues of schweifurthins have also similar cytotoxicity as naturally occurring ones.

Keywords: Cancer cells; Macaranga; Flavonoids; Stilbenes; Cytotoxic; Schweifurthins.

Introduction

Natural product chemistry has been a topic of great interest since ancient times, being relevant to the preparation of food stuff, coloring matters, fibers, toxins, medicine etc. Separation methods for the study of natural products have been developed and, without doubt, have greatly stimulated the development of the refined techniques used today, such as the various analytical and preparative chromatographic methods. These methods have made it possible for the isolation of extremely small quantities of compounds. Instruments used for the structural determination of compounds such as UV, IR, NMR and MS have been developed and refined rapidly [1,2]. The Plant Kingdom is an important source of chemical compounds. Compounds such as carbohydrates, amino acids and proteins are classified as primary metabolites, while alkaloids, terpenoids, saponins, steroids, flavonoids, and phenolic and like are classified as secondary metabolites. Such metabolites are essential to plant life, many of them providing a defense mechanism against bacterial, viral and fungal attack and are also analogous to the immune system of animals. Genus Macaranga is the source of variety of natural products that are used as therapeutic purpose [1-3].

The genus Macaranga belongs to the family Euphorbiaceae that contains more than 308 species [3] and these plants are shrubs or trees that grows up to 15 m tall. Members of this genus are known for their mutual associations with ants which give benefit for them by attacking or feeding on herbivorous insect. In folk medicine, traditional healers use fresh or dried leaves of some Macaranga species to treat swellings, cuts, sores, boils and bruises [4].

A phytochemical review of many literatures indicates that genus Macaranga is rich source of the isoprenylated, geranylated and farnesylated flavonoids and stilbenes [7]. Furthermore, more classes of secondary metabolites like terpenes, tannins, coumarins [4] and other types of compounds are known to be isolated from different species of the genus. Flavonoids and stilbenes are one of the major constituents and are most likely responsible for most of the activities found in the plants of this genus [5]. An increasing number of phytochemical studies are being carried out on plants belonging to the genus due to their various traditional uses. Thus, the isolated natural products from this genus have been reported to display interesting biological activities including antitumor [6,7], cytotoxic, antioxidant, antimicrobial and anti-inflammatory.

In this genus only 26 species including M Alnifolia, M Barteri, M Bicolour, M Conifer, M Denticulata, M Gigantea, M Gigantifolia, M Hemsleyana, M Indica, M Kurzii, M Lowii, M Mappa, M Monandra, M Peltata, M Pleiostemon, M Pruinosa, M Recurvata, M Rhizinoides, M Ampsonii, M Schweinfurthii, M Sinensis, M Tanarius, M Trichocarpa, M Triloba and M Vedeliana have been investigated phytochemically [8]. About 190 secondary metabolites have been isolated and identified from this genus. The isolated compounds include flavonoids, stilbenes, tannins, terpenes. coumarins, steroids and other types of compounds. About 90% of the isolated compounds have been reported from the leaves while only 10% is from the other parts [8,9].

Pharmacological studies of genus Macaranga indicate the potential of extracts and pure compounds to display specific medical effects. Investigation on the chemistry and pharmacology of this genus showed that its crude extracts and compounds displayed interesting biological activities including anticancer [6,7] and many another biological activities like antifungal, antiviral, antibacterial, antioxidant, antitumor, anti-inflammatory etc [8].

There for the goal of this review paper to assess and evaluates the scientific evidence for the therapeutic claims for Macaranga species in cytotoxicity medical use and summarizes some of species that contains cytotoxic chemical constituents and shows the total synthesis of naturally occurring schweinfurthins anagoueous.

Cytotoxic phytochemicals isolated from genus macaranga

Materials and methods

Different literature materials are used for references and source of data. Journals, Google scholars, websites, published thesis papers and other literature materials were used for source of information

Introduction to cytotoxic chemicals

Cytotoxic chemicals (drugs) describe a group of medicines that contain chemicals which are toxic to immune cells, preventing their replication or growth, and so are used to treat cancer. They can also be used to treat a number of other disorders such as rheumatoid arthritis and multiple sclerosis. Once inside the body, their action is not generally tightly targeted, and they can produce side effects both to the patients and others who become exposed [11].

Anticancer activity

Cancer is abnormal growth of tissue or cell in which the cell grows spreads and divides in uncontrolled way. Also it is called malignancy. Some cancers may eventually spread into other tissues. Cancer starts when gene changes make one cell or a few cells begin to grow and multiply too much. This may result a growth called a tumor. There are more than 200 types of cancer, including breast cancer, skin cancer, lung cancer, colon cancer, prostate cancer, and lymphoma. Symptoms vary depending on the type.

According [11] based on cell type cancer can group in to five main types as follows;

i. **Carcinoma** - Cancer that begins in the skin or in tissues that line or cover internal organs. There are different sub-types, including adenocarcinoma, basal cell carcinoma, squamous cell carcinoma and transitional cell carcinoma.

ii. **Sarcoma** - Cancer that begins in the connective or supportive tissues such as bone, cartilage, fat, muscle or blood vessels.

iii. **Leukemia** - Cancer that starts in blood forming tissue such as the bone marrow and causes abnormal blood cells to be produced and go into the blood.

iv. **Lymphoma and myeloma** - Cancers that begin in the cells of the immune system open a glossary item

v. **Brain and spinal cord cancers** - These are known as central nervous system cancers.

Cancer treatment may include chemotherapy, radiation, and/or surgery [11]. Many cancers are cured. But in some people cancer can return. Some cancers can’t be cured but treatment is often able to control them for some years. Chemotherapy is one of the treatments that use of any drug to treat any disease. But to most people, the word chemotherapy means drugs used for cancer treatment. It’s often shortened to “chemo” Surgery and radiation therapy remove, kill, or damage cancer cells in a certain area, but chemo can work throughout the whole body. This means chemo can kill cancer cells that have spread to parts of the body far away from the original (primary) tumor. The main goal of chemotherapy treatment is cure, if possible to destroy, control, if cure is not possible that prevent growth and spread by shrinking tumor and palliation, when the cancer is in advanced condition, meaning it’s not under control and has spread from where it started to other parts of the body, the goal may be to improve the quality of life or help the person feel better. Palliative care is used to treatment that’s used to reduce symptoms or improve comfort [11-13].

Class of compounds isolated from macaranga genus

Some of cytotoxic chemicals and species that contains cycotoxic chemicals from this genus includes apigenin (1) from M Gigantifolia [14], flavonoids and flavones most of them are prenylated from M Triloba [15], M Denticulata [5], M Indica [16], M Adenantha [17], M Hispida [18], M Lowii [19], flavonoids and stilbene derivatives from M Pruinosa, M Recurvata, M Rhizinoides and M Trichocarpa [20], bibenzyls and flavonoids from M...
Kurzi, prenylated stilbenes from M. Tanarus [3], M. Siamensis and M. Alinofolia and geranyl (two isoprene unit) stilbenes from M. Schweinfurthii [21]. Many of the cytotoxic chemicals from the genus are prenylated (one isoprene unit) flavonoids and stilbenes (2, 11, 12, 13, 16-18 and 21-23) and some of them are geranylated (6, 10, 19 and 24-28) and transylated (three isoprene unit) (8, 9, 20) [8].

Some cytotoxic chemicals from genus macaranga and their cytotoxicity

Genus Macaranga is the rich source of natural products which have variety of biological active compounds that are used for treat different types of diseases. Among the compounds flavonoids and stilbenes are the major constituents. These flavonoids and stilbenes have different cytotoxic activity for different cancer cell lines [8].

Cytotoxic chemical from macaranga gigantifolia

Apigenin (1) a flavonoid compound isolated from Macaranga gigantifolia leaves and have cytotoxic activity against murine leukemia P-388 cell line with potential activity of IC50 (µg/mL) 14.13 [14].

Cytotoxic chemicals from macaranga trilobi

Prenylated, geranylated and farnesylated flavonoids isolated from this plant have been reported to possess several cytotoxic activities. Flavonoids were cytotoxic against three cancer cell lines, namely HL-60 (human leukemia), MCF-7 (human breast cancer), and HeLa (human cervical cancer). The Compounds (2), (3) and (4) showed moderate activity towards HeLa cell lines with IC50 of 12.2, 17.0 and 18.2 respectively and weak activity towards MCF-7 with IC50 22.8, 23.5 and 23.0 respectively. Compound (5) exhibited very strong cytotoxic activity against HeLa and HL-60 with IC50 values of 1.3, 3.3 respectively and strong inhibition against MCF-7 cells with IC50 value 5.6. Compounds (2) and (4) were moderately active against HL-60 cell lines with IC50 value of 15.1 and 11.6, respectively, while (3) weakly inhibited the growth of HL-60 cell line with IC50 21.3 [15].

Cytotoxic chemicals from Macaranga indica

Prenylated, geranylated and farnesylated flavonoids isolated from this plant also have anticancer activity for four human cell lines. Compounds (6-12) showed cytotoxic activity against human breast adenocarcinoma (MCF-7), Human Hepatocellular (HepG2), Human Cervical Carcinoma (Hela) and mouse leukenia (P388) cell lines. Compounds 12, 7 and 9 inhibit the proliferation of MCF-7 cell line with IC50 values of 15.23, 9.74 and 7.88 respectively. Compounds (8) and (11) showed cytotoxic activity against HepG2 cell line with IC50 values of 11.84 and 20.35 respectively. Compounds (8) and (11) exhibit cytotoxicity against Hela cell line with IC50 values of 8.71 and 16.06 respectively. Compounds (6) and (12) showed cytotoxicity against P388 cell line with IC50 values of 11.82, 18.94 and 3.27 respectively [16]. The compounds are shown in Scheme 3.

Cytotoxic chemicals from Macaranga adenantha

The prenylated compounds isolated from M. adenantha showed cytotoxic activity in human cell lines. The prenyl moieties shows promising biological activities due to further modification by cyclization and hydroxylation resulted in the chemical diversity of the prenylated products. The compounds (13-15) are modified prenyl cytotoxic chemicals that are active against two cancer cell lines HepG2 and Hela except (13) which have no anticancer activity. The compounds (14) and (15) exhibits cytotoxic activities against HepG2 cell line with IC50 values of 13.76 and 22.27 respectively. Compound (15) exhibit cytotoxic activity against Hela cell line with IC50 value of 16.18 [17].

Cytotoxic chemicals from Macaranga tanarius

Cytotoxic prenylated, geranylated and farnesylated stilbenes of the schweinfurthins series isolated from fruits of Macaranga tanarius are schweinfurthins (16-20). In addition to these compounds (21-22) are also isolated from this species. The compounds (16-20) showed cytotoxic activities in the Nano molar to sub-micro molar range on U87 glioblastoma cell line, but only compounds (16) and (20) were active on the A549 cell line in the sub-micro molar range. While compounds (21,22) do not show any anticancer activities on these cell lines [3].
Geranylated stilbenes are isolated from *Macaranga scheuferthii* and this phytochemicals shows different cytotoxicity against many types of human cell cancer lines. For the first time schweifurthins are isolated from this species. Compounds (23) and (24) are cytotoxic in the 60-cell line human tumor cancer screen. Schweinfurthin A (23) showed a mean panel IC50 of 0.36, while schweinfurthin B (24) was slightly less potent, giving a mean panel IC50 of 0.81. The brain tumor (CNS) subpanel was the most sensitive to both compounds, while the ovarian cancer cell lines were uniformly resistant. Other sensitive lines to compounds (23) and (24) are leukemia, lung, CNS, renal and breast cancers lines. But compound (25) (schweinfurthin C) is inactive to this cell lines due to lack of hexahydroxanthate ring, which is the pharmacore (reactive part) of the schwefurthins in addition to stilbene functional group [21].
ety of strategies for formation of a 3-keto compound. Reduction of the R, β-unsaturated ketone compound (44) produced alcohol (45) with the desired configuration at the C-2 position. To prevent potential side reactions, the hindered alcohol (45) was protected by MOM to give (46). This compound is oxidized with KMnO4 in acetone to produce (47). Ketone (47) was reduced upon treatment with NaBH4 in quantitative yield to afford alcohol (48). Exposing of compound (48) to DDQ provided aldehyde (49) directly from the methyl ether. Exposing compound (48) to acid hydrolysis and DDQ deprotection gives (50) and alcohol groups are protected by acetone to yield intermediate (31). Aldehyde (49) then was coupled to known phosphonate, which is synthesized from commercially available (51) dihydroxybenzoic acid in 9 steps (Scheme11) or aldehyde (31) is condensed with (32) in the presence of NaH to yield protected stilbene. Finally, acidic hydrolysis of the three MOM acetal or two MOM acetals and hemiacetal under standard conditions provided Schweinfurthin B in moderate yield. Synthetic swweinfurthin B showed to be identical with an authentic sample of the natural material in all respects including specific rotation [21, 22].

**Conclusion**

The Plant Kingdom is an important source of chemical compounds that they have pharmacological activities for treating different disease. Genus Macaranga is the largest member of family Euphorbiaceae and different species from this genus have variety class of secondary metabolities that are used for different therapeutic purposes. Flavonoids and stilbenes are the major compounds which are isolated from different species of Macaranga. These compounds are cytotoxic to different cancer cell lines like human derived lung Adenocarcinoma (A549) Human Breast Adenocarcinoma (MCF-7), Human Hepatocellular (HepG2), Human Cervical Carcinoma (Hela) glioblastoma(U87) and mouse leukemia (P388) cell lines with high to low cytotoxic activities.

Shweinfurthins are stilbenes that are isolated from various Macaranga species in small quantities. These compounds showed different cytotoxic activity based on the National Cancer Institutes (NCI) 60-cell line assay. The scarcity of these natural products has hindered biological evaluation leads to synthesis of the natural product shweinfurthins and their synthetic analogues. The synthetic shweinfurthin B shows almost identical in all respects to naturally obtained shweinfurthin B (21-22).

**References**


