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Revisión / Review

Dicranopteris linearis
A potential medicinal plant with anticancer properties

[*Dicranopteris linearis*. Una planta medicinal potencial con propiedades anticancerígenas]

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Abstract: Several investigations have demonstrated *Dicranopteris linearis* (Burm.f.) Underw. (Gleicheniaceae) plant extracts possess numerous health-promoting properties. This review is aimed to summarize and highlight the potential possess by *D. linearis* to be developed into future pharmacological entity especially as anticancer agent. This study used several electronic search engines to compile and integrate a number of scientific publications related with *D. linearis*. Scientifically, *D. linearis* has been reported to have antinociceptive, anti-inflammatory, antipyretic, chemopreventive and antioxidant properties which can be linked to its potential to treat various kinds of ailments including inflammatory-related diseases and cancer. A number of scientific evidences related with anticancer studies suggested the ability of *D. linearis*-based phytochemicals to act as potent anticancer lead compounds. In conclusion, *D. linearis* has the potential to be developed into potent anticancer agent as depicted by a number of isolated phytochemicals which can work synergistically to contribute to its anticancer properties.

Keywords: *Dicranopteris linearis*; Anticancer; Medicinal plant.

Resumen: Varias investigaciones han demostrado que los extractos de la planta *Dicranopteris linearis* (Burm.f.) Underw. (Gleicheniaceae) poseen numerosas propiedades promotoras de la salud. El objetivo de esta revisión es resumir y resaltar el potencial que posee *D. linearis* para convertirse en una entidad farmacológica futura, especialmente como agente anticancerígeno. Este estudio utilizó varios motores de búsqueda electrónicos para compilar e integrar una serie de publicaciones científicas relacionadas con *D. linearis*. Científicamente, se ha informado que *D. linearis* tiene propiedades antinociceptivas, antiinflamatorias, antipiréticas, quimiopreventivas y antioxidantes que pueden estar vinculadas a su potencial para tratar varios tipos de dolencias, incluidas las enfermedades asociadas a inflamación y el cáncer. Una serie de evidencias científicas relacionadas con los estudios anticancerosos sugirieron la capacidad de los fitoquímicos basados en *D. linearis* para actuar como potentes compuestos anticancerígenos. En conclusión, *D. linearis* tiene el potencial de convertirse en una fuente de potentes agentes anticancerígeno, como se describe en una serie de fitoquímicos aislados que pueden actuar de forma sinérgica para contribuir a sus propiedades anticancerígenas.

Palabras clave: *Dicranopteris linearis*; Anticancerígeno; planta medicinal.

INTRODUCTION

Cancer is a disease that is associated with abnormal uncontrolled cell growth that is caused by loss of cell cycle control. Chemotherapy, radiotherapy, hormone therapy and surgery have been the mainstays of cancer treatment for many years (Levine & Centre, 2010). Chemotherapy drugs that are mostly used to treat cancer patients are antimetabolites (e.g. methotrexate), antitubulin agents (e.g. taxanes), DNA-interactive agents (e.g. cisplatin, doxorubicin), hormones and molecular targeting agents (Nussbaumer *et al*., 2011). However chemotherapy is highly inadequate due to the lack of cytotoxic drug specificity (Buolamwini, 1999; Rebbaa, 2005) and the consequent generation of toxic side effects when high doses are administered (Rebbaa, 2005). Clinical uses of chemotherapy drugs have been proven to associate with several undesirable effects such as hair loss, gastrointestinal lesions, drug resistance, suppression of bone marrow, neurologic dysfunction and cardiac toxicity (Monsuez *et al*., 2010; Dropcho, 2011; Nussbaumer *et al*., 2011). For this reason, the explorations for new anticancer agents that possess better efficacy with minor side effects are extensively been carried out worldwide.

Natural compounds are known to be a good source in the development of new therapy that can treat various diseases since the undesirable after-effects is lesser compared to synthetic drugs (Stankovic *et al*., 2011). Based on the experimental reports, several medicinal plants and herbal ingredients have been found to possess potential anticancer effects, for example fruit extract from *Vatica diospyroides* Symington (Chothiphirat *et al*., 2019); *Althernanthera sessilis* extract (Gothai *et al*., 2018); *Eclipta alba* extracts (Yadav *et al*., 2017) and *Tragopogon porrifolius* extract (Al-Rimawi *et al*., 2016). A part from that, a number of phytochemicals that were successfully isolated from medicinal plants also have been found to effectively prevent cancer, reduce cancer cell proliferation, induce apoptosis, retard metastasis and inhibit angiogenesis (Afshari *et al*., 2006; Ehsanfar *et al*., 2006; Shu *et al*., 2010; Tan *et al*., 2011; Mortazavian & Ghorbani, 2012; Singh *et al*., 2016; Meybodi *et al*., 2017). The aim of this review is to highlight the potential of a neglected fern named *Dicranopteris linearis* as a valuable plant with anticancer properties, supported with scientific evidence to unravel its beneficial pharmacological properties.

METHODS

This study is a combination of scientific studies and publications gathered from various trustable sources using keywords such as "*Dicranopteris linearis*", "anticancer", "phytochemicals", "cancer", "chemoprevention", "medicinal plant" and "herbal medicine". The trustable sources that had been used are scientific search engines which were PubMed, Scopus, Google Scholar and ScienceDirect. The review information were arranged in a manner from broad to specific subjects, whereby towards the end of the review, the focus was given on the pharmacological properties that support the plant's anticancer potential.

History of medicinal plant

Medicinal plants have been used by mankind as a source of medicines since primordial. Information on the ancient uses of plant materials as medicines can be found in archeological finds, old literature, history books and pharmacopoeias. Terrestrial plants have been used in Egypt, China, India and Greece since ancient times and have developed an impressive number of modern drugs. The first written records on the medicinal uses of plants were from the Sumerians and Akkaidians which appeared around 2600 BC (Samuelsson, 1999).

However, the number could be much higher as knowledge on the indigenous uses of plants was mostly passed on orally from one generation to another and remained undocumented (Jantan, 2004). Over the past decades, herbal medicine has become a topic of global importance, making an impact on both world health and international trade thus play a central role in the healthcare system of large proportions of the world's population (Dixit & Ali, 2010). It is estimated that 80% of the people in the world's developing countries rely on traditional medicine for their primary health care needs, and about 85% of traditional medicine involves the use of plant extracts (Nalawade *et al*., 2003). Plants are considered among the main sources of biologically active chemicals. It has been estimated that about 50% of the prescription products in Europe and USA are originating from natural products or their derivatives (Newman *et al*., 2003). More than 35,000 plant species have been reported to be used around the world for medicinal purposes, with only 15% of the total have been studied for their pharmacological properties (De Luca, 2012; Palhares, 2015). Previously, the use of plants as medicines has involved the isolation of active compounds,

beginning with the isolation of morphine from opium in the early 19th century (Samuelsson, 1999; Kinghorn, 2001).

Medicinal plant in anticancer therapy

Lately, medicinal plants involve as an essential position for being the predominant sources of drug discovery, regardless of its classified groups of herb, shrub or tree. Plants have been an imperative source in treating various types of illnesses including cancer. World Health Organization reported that 80% of the people who lived in the provincial areas rely upon medicinal plants as their elemental health care system. These practices are exclusively in view of the learning of conventional utilization of medicinal plants. Development of natural products is performed to create different type of drugs that are efficient in enhancing the anticancer activities. Profound understanding of the complex synergistic connection of different constituents of anticancer herbs, would definitely help in defining the plan to attack the malignant cells without harming the normal cells in the body (Merina *et al*., 2012; Palhares *et al*., 2015). The National Cancer Institute has collected around 25,000 plant samples from 20 different countries and has screened 114,000 plant extracts for their anticancer activity (Shoeb, 2006). Along with that, more than 3000 plant species have been accounted to have antitumor properties (Chanda & Nagani, 2013).

Natural products still remain as a major source of drug candidate and drug lead, as previously estimated that 25% of modern drugs and 60% of antitumor drugs are derived from natural products (Newman & Cragg, 2012). According to Cragg & Newman (2000), more than 50% of the medication in clinical trials that were tested for anticancer properties were isolated from natural sources. Several anticancer agents that were derived from plants include podophyllotoxin, taxol, vincristine and camptothecin (Pezzuto, 1997). Each of the anticancer drugs occupies their unique mechanism of actions towards the cancer cells; this includes interaction with microtubules (Gordaliza *et al*., 2007), inhibition of topoisomerases I or II, alkylation of DNA, and interference with tumour signal transduction (Nobili *et al*., 2009).

Dicranopteris linearis

Figure No. 1
***Dicranopteris linearis* Fern**

Dicranopteris linearis (Figure No. 1), is a type of commonly found fern that belongs to the family Gleicheniaceae, and known locally to the Malays as “Resam” (Derus, 1998), “uluhe” to the Hawaiians, and “dilim” to the Filipinos (Russel *et al*., 1998). *D. linearis* is common in secondary forests

and grows well on poor clay soils. It is a plant that is considered primitive that instantaneously grows into thickets of about 2 meter tall, shading out the other plants (Chin, 1993). As one of the most widely distributed fern that easily grow in wet climate, the distribution of *D. linearis* are common in regions like Asia, Polynesia, Africa, Europe and the Pacific (Figure No. 2) (Russel *et al*., 1998).

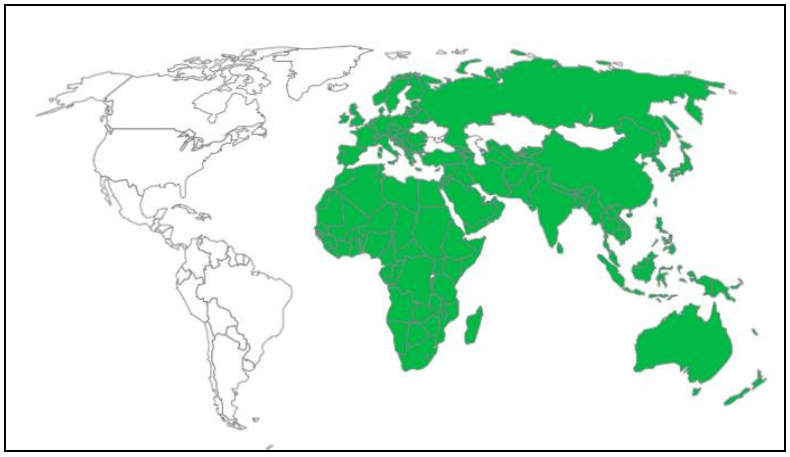

Figure No. 2
Distribution map of *D. linearis* worldwide (represented by areas coloured in green)

In Southeast Asia, the leaves of *D. linearis* were traditionally used to reduce body temperature and to control fever (Chin, 1992; Derus, 1998). However, on the basis of literature search, information on the traditional usage of *D. linearis* around the world are limited, with only three reports describing its use in treating external wounds, ulcers, and boils by the people of Papua New Guinea, getting rid of intestinal worms by the people of Indochina (Chin, 1992), and to treat asthma and women's sterility by the tribes on an Indian mountain (Vasuda, 1999).

Phytochemical profile of *D. linearis*

D. linearis is under the family of Gleicheniaceae, which consist of approximately 120 primitive ferns species. The segregation of Gleicheniaceae family is supported by the distribution of flavonol-3-O-glycosides, sensu lato, into at least three groupings (Wallace *et al*., 1983). Terpenoids (which include labdane-type and clerodane-type diterpenoids, diterpenoid glycosides and triterpenoids) and flavonoids (which include flavonol glycosides) are two most common phytochemicals found in Gleicheniaceae family (Cao *et al*., 2017). Another study by Raja *et al*., (1995) found a glycoside, (6*S*,13*S*)-6-[6-*O*-acetyl-beta-D-glucopyranosyl-(1-->4)-alpha-L-rhamnopyranosyloxy]-13-[alpha-L-rhamnopyranosyl-(1-->4)-beta-D-fucopyranosyloxy]-cleroda-3,14-diene which is common in *Dicranopteris* species and can be regarded as a chemical marker for this genus group. Other than that, depending on the varieties of the fern used, *D. linearis* also had been reported to contain afzelin, quercitrin, isoquercitrin, astragalin, rutin and kaempferol 3-*O*-(4-*O*-*p*-coumaroyl-3-*O*-alpha-L-rhamnopyranosyl)-alpha-L-rhamnopyranosyl- (1-->6)-beta-D-glucopyranoside.

Phytochemical screening of *D. linearis* leaves have been mainly done by using the dried powdered form and extracts form of different solvents. Based on previous studies, *D. linearis* in dried powder form and extracts form of aqueous, chloroform and methanol revealed the presence of flavonoids, saponins, tannins, steroids, and triterpenes (Zakaria *et al*., 2006; Zakaria *et al*., 2008; Zakaria *et al*., 2011; Rodzi *et al*., 2013; Kamisan *et al*., 2014), with the aqueous extract contained mainly saponins and triterpenes (Zakaria *et al*., 2019).

All of the isolated phytochemicals, which

have previously been extracted from various plants of different origin, have been reported to possess antitumor activity via diverse mechanisms. For example, flavonoids antitumor activity has been associated with various anticancer mechanisms such as the modulation of cell cycle arrest at the G_1/S phase, induction of cyclin-dependent kinase inhibitors, down regulation of anti-apoptotic gene products, inhibition of cell-survival kinase inhibition of inflammatory transcription factors as well as induction of Ca^{2+}-dependent apoptotic mechanism (Chahar *et al*., 2011). On the other hand, saponins have been reported to induce apoptosis by causing permeabilization of the mitochondrial membranes (Lemeshko *et al*., 2006) or necrotic cell death depending on the types of cancer cells (Russo *et al*., 2005). Triterpenes were also found to cause cell cycle disruption via diverse mechanisms, one of them is by decreasing the number of cells in G_0/G_1 phase, with initial increases in S and G_2/M (Roy *et al*., 2006) or by inhibiting nuclear factor-kappa B (NF-κB) (Lee *et al*., 2006).

UHPLC-ESI/HRMS and GC-MS profile of *D. linearis* methanolic extract.

Based on the UHPLC-ESI/HRMS analysis conducted by Zakaria *et al.* (2017), 5 major compounds were detected in the methanolic extract of *D. linearis* (MEDL) which are known as apigenin-7-O-glucoside, ferulic acid hexose, catechin, rutin and gallic acid.

As for the GC-MS analysis, forty eight volatile compounds were identified in MEDL with triphenylphosphine oxide (17.52%), methyl-9,12,15-octadecatrienoate (13.43%), methyl palmitate (9.70%), 3,4-Pyridinedicarboxylic acid, 6- (4-chlorophenyl)-, dimethyl ester (7.98%), erucylamide (5.45%), 5,10-Dihexyl-5,10-diihydroindolo[3,2-b]indole-2,7- dicarbaldehyde (4.63%) and methyl linoleate (4.17%) were identified as the major volatile compounds. However, only methyl palmitate, methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate, and shikimic acid were reported to exert antioxidant activities (Zakaria *et al*., 2017). Table No. 1 outlined the isolated compounds from both UHPLC-ESI/HRMS and GC-MS analysis with anticancer, antioxidant and/or cytotoxic activities, which are highlighted here as the main focus of the current review.

Table No. 1
Major compounds detected in methanol extract of *Dicranopteris linearis* (MEDL) with reported anticancer, antioxidant and/or cytotoxic activities

Major compounds detected in MEDL	Previous reports on anticancer, antioxidant and/or cytotoxic activities
Apigenin-7-O-glucoside	• Antioxidant, cytotoxic (Smiljkovic *et al*., 2017)
Ferulic acid hexose	• Antioxidant (Graf, 1992)
Catechin	• Antioxidant (Higdon & Frei, 2003; Chobot *et al*., 2016)
Rutin	• Antioxidant, anticancer (Ganeshpurkar & Saluja, 2017)
Gallic acid	• Antioxidant, anticancer (Subramanian *et al*., 2015)
Methyl palmitate	• Antioxidant (Zakaria *et al*., 2017)
Methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate	• Antioxidant (Zakaria *et al*., 2017)
Shikimic acid	• Antioxidant (Zakaria *et al*., 2017)

Other major compounds of MEDL which have not been reported previously to have antioxidant, anticancer and/or cytotoxic activities, are not cited here for their pharmacological properties.

To date, one phytochemical compound which had been found to be the specific chemical marker for *Dicranopteris* species [which is (6*S*,13*S*)-6-[6-*O*-acetyl-beta-D-glucopyranosyl-(1-->4)-alpha-L-rhamnopyranosyloxy]-13-[alpha-L-rhamnopyranosyl-(1-->4)-beta-D-fucopyranosyloxy]-cleroda-3,14-diene] (Raja *et al*., 1995) has never been tested for any pharmacological property. Thus, the anticancer property of this specific *Dicranopteris*-based glycoside cannot be outlined, which warrant further study to be carried out to delineate potential anticancer activity of the glycoside. Nevertheless,

there are increasing results showing a number of naturally occurring glycosides isolated from diverse plant species possessed marked anticancer activity against a variety of cancer cell lines in initial preclinical studies (reviewed by Khan *et al*., 2019). This highlight the potential of the specific glycoside isolated from *Dicranopteris* which might also has the ability to combat cancer cells and become interesting drug candidate for anticancer therapy.

Other pharmacological activities of D. linearis

A vast number of studies has been carried out to study the pharmacological effects of *D. linearis* against various diseases. Extracts of *D. linearis* of different polarity have been used in the quest of determining the most effective *D. linearis* treatment against various ailments. Scientific studies demonstrated that *D. linearis* extracts possessed antinociceptive, anti-inflammatory and antipyretic activities (Zakaria *et al.*, 2008), antibacterial activity (Lai *et al.*, 2009), and potential cytotoxic and antioxidant activities against various types of cancer cells (Zakaria *et al.*, 2011). However, further discussion on pharmacological activities of *D. linearis* other than its anticancer-related activities is beyond the scope of this review.

Cytotoxic and antioxidant activities of D. linearis

The link between antioxidant, anti-inflammatory and anticancer activities of plant extracts have been strongly acknowledged. Multiple studies, both epidemiological and experimental, suggest that plant extracts may contribute to the prevention and possibly the treatment of chronic diseases such as cancer (Chohan *et al*., 2012). Therefore, plant extract which possessed both antioxidant and anti-inflammatory properties is highly desirable due to their ability to combat free-radical-mediated peroxidation of membrane lipids and proteins. These are believed to be closely associated with a variety of chronic pathological complications such as cancer, atherosclerosis, and neurodegenerative diseases. Since inflammation and oxidation processes are also closely linked to tumour promotion, initiation and progression, plant extract with potent anti-inflammatory and antioxidant properties is anticipated to exert chemo preventive effects on carcinogenesis (Balasubramaniam & Ragunathan, 2012).

Cytotoxicity study was carried out by screening the cytotoxic effects of *D. linearis* extracts against a panel of cancer cell lines by using 3,(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. A study by Zakaria *et al*. (2011) demonstrated the effects of aqueous (AEDL), chloroform (CEDL) and methanolic (MEDL) extracts of *D. linearis* against acute promyelocytic leukemia (HL-60), breast adenocarcinoma (MCF-7) and (MDA-MB-231), cervical carcinoma (HeLa), chronic myelogenous leukemia (K-562), and colorectal adenocarcinoma (HT-29) cancer cell lines. This study reported that MEDL showed significant cytotoxicity effects against MCF-7, HeLa, HL-60, K-562 and MDA-MB-231 cancer cell lines, while the CEDL only showed significant cytotoxicity effects against MCF-7, K-562, HL-60 and HeLa cancer cell lines. However, both MEDL and CEDL failed to show cytotoxic effects against HT29 cancer cells. On the other hand, the AEDL did not show cytotoxic activity against all of the cancer cell lines studied. Another study by Rodzi *et al*. (2013) revealed the chemopreventive potential of methanolic extract of *D. linearis* (MEDL) on chemical-induced carcinogenesis. In the study, MEDL showed a dose-dependent anti-carcinogenic effect on topical application of 7,12-dimethylbenz[a]anthracene (DMBA) as tumor inducer and croton oil as tumor promoter on ICR female mice. The MEDL was found to significantly reduced tumor formation, tumor burden, tumor volume and tumor incidence. At the same time, tumor latency was also increased which signifies the increased time taken for tumor to develop with every application of MEDL, compared to control mice. This study highlighted the ability of *D. linearis* to serve as a potential medicinal plant with good chemopreventive effect.

The results were further supported with a study by Baharuddin *et al*. (2018) that exhibited the ability of methanolic extract of *D. linearis* to inhibit the proliferation of human breast cancer cell line (MDA-MB-231) via induction of S-phase arrest and apoptosis. In the study, MTT proliferation assay showed that *D.linearis* extract inhibited MDA-MB-231 cancer cell growth in a time dependent manner. Further studies using phase contrast and fluorescence microscopy examinations indicated that *D.linearis* extract was able to induce apoptosis in MDA-MB-231 cells. Cell cycle analysis revealed that *D.linearis* extract could induced S phase cell cycle arrest in MDA-MB-231 cells effectively after 72 hours incubation. Early apoptosis induction in MDA-MB-231 cells was confirmed by Annexin V-FITC and PI staining. Significant increase in apoptotic cells were

detected after only 24 hours of treatment with *D. linearis* extract with 15.1% cells undergoing apoptosis, and the amount of the apoptotic cells escalated to 18.3% as the incubation period with MEDL were prolonged to 48 hours. These findings suggested that *D. linearis* extract has potential as a potent cytotoxic agent against MDA-MB-231 cancer cell lines.

On the other hand, the antioxidant activity of *D. linearis* which was carried out by Zakaria *et al*. (2011) was assessed using the DPPH radical and superoxide scavenging assays. The antioxidant activities of AEDL (aqueous extract of *D. linearis*), CEDL (chloroform extract of *D. linearis*) and MEDL were tested by using concentrations of 20, 100 and 500 µg/mL of the respective extracts. Results showed that MEDL produced the highest antioxidant activity (between 37.8 - 99.7%) in the DPPH radical scavenging test compared to the AEDL (29.3 - 94.3%) and CEDL (13.3 - 66.1%). In addition, MEDL also demonstrated the highest activity in the superoxide scavenging test with activity ranging between 84.2 - 99.7% as compared to the AEDL (62.1 - 97.4%) and CEDL (33.2 - 71.7%).

The chemical components of medicinal plants mainly possess antioxidant properties that contribute to their anticancer potential. Flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignans, catechins, and isocatechins are the major classes of bioactive constituents responsible for the antioxidant action (Nema *et al*., 2013). Previous study had proven that the flavonoids content in various plants have high free radical scavenging activity. The flavonoids also demonstrated an effective cytotoxicity activity against a series of human cancer cells which includes the human cancer cells (A456), hepatoma (HepG2), cervical carcinoma (Hela) and breast cancer (MCF-7) (Cao *et al*., 2013; Wen *et al*., 2014). Based on these findings, it is possible that flavonoids in *D. linearis* have the capability to inhibit the growth of cancer cells.

CONCLUSION

Dicranopteris linearis is a neglected plant, which increasingly showing strong evidence and high potential to treat various kind of diseases, including cancer. Its ability to inhibit the progression of cancer cells had been documented, and supported with other pharmacological studies, such as antioxidant, anti-inflammatory, antinociceptive and chemopreventive properties. Those properties have been acknowledged to have significant and strong relationship with anti-cancer properties. Current findings related with *D. linearis* anticancer properties might also resulted from the pharmacological activities of various *D. linearis*-based phytochemicals, which may work individually or synergistically to produce the anticancer effects. Further study is needed to delineate the anticancer mechanisms of the plant, together with detail investigation on the isolation and identification of bioactive compounds responsible for its anticancer property. It is hoped that *D. linearis*-based bioactive compounds can become as one of the alternative treatment to overcome the adverse effects produced by current chemotherapy agents, thus support the findings that suggest *D. linearis* as a potential medicinal plant to be developed into useful anticancer agent candidate with better efficacy and specificity.

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