Available online freely at www.isisn.org

Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

REVIEW ARTICLE BIOSCIENCE RESEARCH, 2021 18(4): 2830-2844. **OPEN ACCESS**

Hedyotis-Oldenlandia genus: A review of Traditional Chinese Medicine herb

Sulaiman Ngadiran[1], Maizatulakmal Yahayu[1], Siti Zulaiha Hanapi[1], Ida Madiha Yusoff[1], Siti Hajar Mat Sarip[1], Roslinda Abd Malek[1], Mohd Faizal Mohamad[1], Low Hock Heng[2], Er Kian[2]and Hesham A. El Enshasy[1.3,4*]

[1]Institute of Bioproduct Development (IBD), Universiti Teknologi Malaysia (UTM), Johor Bahru, Johor**, Malaysia**
[2]ESE Wood Sdn. Bhd., Johor Bahru, Johor, **Malaysia**
[3]School of Chemical and Energy Engineering, Faculty of Engineering, Universiti Teknologi Malaysia (UTM), Johor Bahru, Johor, **Malaysia**
[4]City of Scientific Research and Technology Applications (SRTA), New Burg Al Arab, Alexandria**, Egypt**

***Correspondence:** henshasy@ibd.utm.my **Received: 19-06-2021, Revised: 29- 10-00-2021, Accepted: 08-10-2021 e-Published: 16-10-2021**

Members of Rubiaceae family are a rich source of secondary metabolites existing as pure compounds or standardized crude extracts. It has provided a wide range of opportunities for the exploration and discovery of new drugs. *Hedyotis* or *Oldenlandia* is one of the important members of this family and has shown multifunctional pharmacological properties according to continuous scientific research conducted on that plant genus since last few decades. The justification of use of *Hedyotis-Oldenlandia* in folk medicine is supported by its reported biological activities including anticancer, antioxidant, antidiabetic, anti-inflammatory and antimicrobial activities. This genus also has been recognized to be abundant with bioactive phenolic compounds, proteins, carbohydrates, steroids and terpenoids. Therefore, this review highlights the traditional uses, phytochemical profiling and phenolic contents, pharmacological review and structure-activity relationship of chemical constituents in *Hedyotis-Oldenlandia* plants. However, further studies are still required to explore the molecular targets responsible for the reported pharmacological properties in order to establish a comprehensive profile of the isolated compounds before proceeding with further clinical trials.

Keywords: *Hedyotis-Oldenlandia*; Rubiaceae, phenolic compounds; biological activities; pharmacological properties

INTRODUCTION

Hedyotis or *Oldenlandia* L. plant genus is a weedy folk herb which is widely distributed in the tropical and warmer regions around the world such as China, Japan, Vietnam, India, Indonesia and Thailand. This Rubiaceae plant family consists of more than 700 species and is well-known in Traditional Chinese Medicine to treat some inflammation-linked diseases likes appendicitis, hepatitis, tonsillitis and urethritis since years (Guo et al. 2013; Neupane et al. 2015). Amongst all, *Hedyotis corymbosa* is the most popular species which is commonly being used as an active ingredient in traditional herbal medicine.

In traditional medicine, this plant genus is broadly used in Ayurveda, Unani, and Siddah, where most of *Oldenlandia* species are managed to cure or treat different diseases. For centuries, various parts of *Hedyotis-Oldenlandia* genus such as aerial parts, roots, and whole plants, have long been consumed therapeutically in Asia region due to their broad spectrum of pharmaceutical activities to treat various illnesses (Sahu et al.

2020; Artanti et al. 2015; Das et al. 2019). The seeds, berries, rhizomes part, leaves, bark, flower, or even whole seeds of plants are used in herbal therapy (Pan et al. 2014). The processing approach for traditional preparation of this herbal is by decoction, tincture, powders, poultice, paste and others (Das et al. 2019; Quattrocchi, 2012; De Zoysa et al. 2017; Félix-Silva et al. 2017; Kadir et al. 2015; Sahu et al. 2020).

Hedyotis-Oldenlandia complex shares the following common morphology and traits: herbs or shrubs, 4-merous flowers, bilobed stigmas, bilocular and many seeded capsules (Neupane et al. 2009; Guo et la., 2013). Scientifically, this genus has been reported to contain numerous bioactive constituents such as iridoids, anthraquinones, flavonoids, alkaloids, sterols and polysaccharides (Nguyen et al. 2018; Mahibalan et al. 2016). Recent pharmacological studies on this plant genus have revealed the potential use of this plant compounds and extracts as antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic, hepatoprotective and neuro protective activities (Nguyen et al. 2018; Yang et al. 2008; Chua, 2013).

Traditional uses of the genus

In total 21,000 plants are classified under WHO and are commonly used throughout the world for medicinal purposes since immemorial time (Anand et al. 2019). *Hedyotis-Oldenlandia* genus is considered as a vast prospect fountain of medicinal assessment, regarding phytochemical studies and bioactivities (Zhang et al. 2017; Hu et al. 2015; Yousef et al. 2018; Sahu et al.2020; Shan et al. 2017; Wang et al. 2018). Therefore, the inherited knowledge, skills, and practices about traditional uses of plants of this genus are based on theories, beliefs, and experiences (practical or by mouth). All was used in the treatment of ailments as well as in the preventive measures and management of physical and mental illness or a folk medicine (Ong et al. 2011; Pan et al. 2014; Suruse et al. 2015).

Oldenlandia corymbosa decoction is an essential cold property herb used in the treatment of fever to eliminate toxins from the body and improve blood circulation (Das et al. 2019; De Zoysa et al. 2017). The herbs were useful to get rid of the body heat. The decoction of the aerial component of this plant is used for cough, bronchitis, leprosy, jaundice, and nervous systems care (De Zoysa et al. 2017). The leaves were collected, clean, pounded, heated and the juice drunk to treat stomach disorders for children or dysentery (Sahu et al. 2020). The plant is effective also to treat sore eyes and viral infections (Sahu et al. 2020; De Zoysa et al. 2017). For the wholesome of the herbs is used in decoction as potential to ease depurative, digestive problem, suffering by diuretic, anthelmintic, pectoral, stomachic, and anti-rheumatic symptom (Table 1) (Sahu et al. 2020). For Indian folk medicine practice, the plant is a common component of internal cure mixtures to alleviate remittent fevers, gastric problems, and as an energy booster or tonic (Das et al. 2019). Besides that, the tincture of the root is testified to have an anthelmintic medicine or vermifuge action. The Chinese practice was discovered the plant useful and functioning well to treat skin sores, sore throat, bronchitis, gynaecologic infections, and pelvic inflammatory (Sahu et al. 2020). The plants are recognized anti-inflammatory medicine with antibacterial properties. In other studies, the whole plant was beneficially used in treating rheumatoid arthritis (Yousef et al. 2018; Ghosh et al. 2015:). In Congo, it is consumed by ready mothers to smooth childbirth. It is also used as a mouth wash in toothache in several countries (Yousef et al. 2018; Chimkode et al. 2009).

Hedyotis umbellata is an Ayurvedic Indian herb powdered leaf and stem bark that is typically used as a medical emergency in the traditional medicine of India and China to against snakebite (Dey and De, 2012). The decoction of the leaves was applied as a cleanse or antidote for poisonous bites. The paste of *Hedyotis scandens* Roxb is made with leaves and stem and externally applied twice a day for 3 to 4 days in a warmed state (Félix-Silva et al. 2017; Kadir et al. 2015). Anti-venomous properties evaluated by laboratories and correlating with ethno pharmacological studies have been found to include herbal related plants and natural products (Dey and De, 2012). The roots decoction is considered as a good expectorant action in treating asthma, bronchitis, bronchial catarrh treatment, and the leaves extracts are used to pamper at an area or poisonous bites (Behera et al. 2018). For other use, the plants of *Oldenlandia* sp were applied as a tenderizer and it is cooked with good synergy with other vegetables such as *Amaranthus* and *Cucurbita*. This species is also known for being a huge source of natural vitamin C (ascorbic acid) (Das et al. 2019) Vitamin C is an important role as an antioxidant that protects the body from free radical damage, protects the immune system, fight off infections and metabolic functions (Chambial et al. 2013). For *Hedyotis umbellata*, especially the roots bark from 2 years old plant was a source of Chay-rot dye, after occupied by mordant for divulging red colour to calico, wool and silk fabrics (Rekha et al. 2006). The practices were performed in various countries by practitioners, tribes, or the society to enhance healing properties and to maintain well-being (Sahu et al. 2020; Das et al. 2019).

Phytochemical review on plant

Phytochemical review of *Hedyotis-Oldenlandia* genus have explored the presence of anthraquinones derivatives, flavonoids and their glycosides, alkaloids, iridoids and their glycosides, saponins, lignans, coumarins derivatives, triterpenoids and sterols (Lajis and Ahmad, 2006; Nguyen et al. 2018; Chen et al. 2018; Song et al. 2019 and Li et al. 2019). From this Rubiaceous family, many natural compounds with the novel structures and extraordinary biological properties from these classes of compounds has been scrutinized (Nguyen et al. 2018).

Previous assessment of *Oldenlandia umbellata* has discovered the existence of a novel symmetrical coumarin dimer and anthraquinones derivatives (Mahibalan et al. 2016, Ramamoorthy et al. 2009), kaempferol-3-*O*-rutinoside and ursolic acid (Hema et al. 2009). The list of secondary metabolites presence from different species of *Hedyotis-Oldenlandia* is presented in Table 2 below.

Total Phenolic Content (TPC) of *Hedyotis-Oldenlandia* sp

The consumers' awareness on health benefits in their diet has led to increase the demand for natural products containing biologically active compounds. Plants such as *Hedyotis-Oldenlandia* have been a valuable source of phenolic contents and antioxidant agents for maintaining human health. The phenolic compounds can be classified into simple phenols, phenolic acids, flavonoids, coumarins, stilbenes, hydrolysable and condensed tannins, lignins and lignans (Kumar and Goel, 2019). The phenolic compounds are produced via shikimic acid pathway in the plant. The basic structure of phenolic compounds comprises of an aromatic ring with one or more –OH groups. In the synthesis of phenolic compounds, the important procedure is the commitment of glucose to the pentose phosphate pathway and transforming glucose 6-phospate irreversibly to ribulose-5-phosphate (Lin et al. 2016). The phenolic compounds are essential for regulating various metabolic functions including as an antioxidant agent. Several studies suggested that phenolic compounds have correlation in trapping the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and might be responsible in antioxidant activities as for inhibiting the harmful effect of oxidative stress by acting as free radical scavenger (Phuyal et al. 2020, Khettal et al. 2016).

To investigate the importance of phenolic contents in *Hedyotis* plants, a study by Christhudas et al. (2013) was conducted. The *H. biflora* was dried and powdered before extracted using methanol, hexane, and ethyl acetate. The powdered *H. biflora* was extracted three times by cold percolation with the ratio 1 kg of dried powder with 3 L of solvent (1:3). The extracts were stored in a refrigerator prior to determination of total phenolic content. The total phenolic contents were determined by spectroscopy method. The absorbance was read at 765 nm. The study showed that the total phenolic contents in *H. biflora* extract was found from 86.89 ± 0.46 to 206.81 ± 1.11 mg of catechol equivalents/g extract. The methanolic extract showed the highest (206.81 ± 1.11 mg of catechol equivalents/g extract) total phenolic content compared to hexane extract (86.89 ± 0.46 mg of catechol equivalents/g extract) and ethyl acetate extract (106.16 ± mg of catechol equivalents/g extract). The results obtained in the study clearly indicate that *H. biflora* has a potential amount of total phenolic content. According to the study, phenolic contents might be play an important role in adsorbing and neutralizing free radicals, quenching singlet and triplet oxygen or decomposing peroxide.

Quercetin is a well-known bioactive compound and polyphenolic flavonoid which can be found in *Hedyotis* plants. A study was conducted by Zhu and Row (2011) on extraction of quercetin from *Oldenlandia diffusa.* In order to increase the quercetin extraction efficiency, the ultrasonic extraction method was applied in this study. The amino-modified active carbon catridges were prepared. Solvent extraction and solid phase extraction were optimised. For the solvent methanol showed as the best solvent in quercetin extraction from *O. diffusa*. The quercetion extraction yield were increased as the extraction time increased from 20 to 60 minutes and ultrasonic power from 20 to 40 W. The optimised extraction yield was 0.198 mg/g. This study was successfully developed an extraction method for quercetin from O. *diffusa* suggested the extraction method for purification of bioactive compounds from natural resources.

Antioxidant properties of *hedyotis-oldenlandia* sp

A study conducted by Ahmad et al. (2005) showed that *Hedyotis* species exhibited strong antioxidant properties compared to Vitamin E. The further study conducted by Sasikumar et al. (2010) regarding to in vitro study antioxidant activities of *Hedyotis corymbosa* (L.) Lam. The aerial parts were used in this study by extracting the plant parts with methanol as solvent. The methanolic extract of *H. corymbosa* was evaporated to dryness by rotary evaporator to ensure the solvent completely removed from extract. The methanolic crude extract of *H. corymbosa* were investigated on the total phenolic contents, total flavonoid contents, DPPH radical scavenging activity, ferric reducing power capacity, scavenging of 2,2'-azinobis-3-ethylbenzothiozoline-6-sulfonic acid (ABTS) radical cation, nitric oxide and hydroxyl radical scavenging activities. The antioxidant activity of the extract was comparable with the standard butylated hydroxyl toluene (BHT). The results showed that *H. corymbosa* has potential as a natural antioxidant agent. This study also recommended the future study to investigate on compound isolation and mechanisms of action for antioxidant activity.

The study on *H. corymbosa* was continued by Endrini in 2011. The results showed that *H. corymbosa* exhibited as a potential antioxidant agent. The methanol was used as a solvent to extract the plant. The study also compared the antioxidant activities of *H*. *corymbosa* with *Pilea trinervia* (Roxb.) Wight. Both plants were extracted to yield about 10% of extract from the original plant samples. The extraction was conducted at room temperature. The samples were filtered through Whatman No.1 and the collected filtrates were evaporated at 40 °C using a rotary evaporated until completely dried. The extracts were subjected to DPPH scavenging activity as DPPH method able to evaluate the scavenging free radical activities in a short time. The *H. corymbosa* showed higher antioxidant activity compared to *P. trinervia.* The results also consistence as *H. corymbosa* also exhibited the highest anticancer activity on MCF-7 cell lines. The recommendation for the further study is to evaluate the mechanisms of action in antioxidant activities as *H. corymbosa* also showed an important and potential property as anticancer agent.

The research conducted by Christhudas et al. (2013) showed that *H. biflora* extract has reductive capabilities compare to butylated hydroxytoluene. The methanolic extract of *H. biflora* was very potent than hexane and ethyl acetate extract. The power of the extract increased with the quantity of sample. The plant extract could reduce the most Fe^{3+} ions which had lesser reductive activity than butylated hydroxytoluene. In DPPH radical scavenging activity of *H. biflora* methanolic extract exhibited a 50% inhibition (IC_{50}) concentration at a concentration of 520.21±1.02 µg/ml. In hydroxyl radical scavenging assay, the concentration for 50% inhibition *H. biflora* was found to be 510.21 µg/ml. For nitric oxide radical inhibition assay, the scavenging activity was increased in a dose-dependent manner. At concentration of 690.20 ± 2.13 µg/ml of extract 50% of nitric oxide generated by incubation was scavenged. From the analyses, the study suggested the methanolic extract of *H. biflora* showed antioxidant properties and might be useful in preventing or slowing the progress of various oxidative stress-related diseases.

The recent study by Das and Bharali (2020) stated that *H. corymbosa* exhibited a promising antioxidant potential against free radical. According to this study, *H. corymbosa* acts as potential antioxidants which are contains substances that having the potential to quench free radicals and significantly delay or inhibit oxidation of the substrate thus protect biological systems against potentially harmful effects of free radicals. The methanol, ethanol, petroleum ether and ethyl acetate were used as solvent to extract and fractionate *H. corymbosa.* The aerial parts and root of *H. corymbosa* were selected and dried at room temperature. The samples were grounded into powder form and undergoes Soxhlet extraction method using 80% ethanol. The extracts were further fractionated using a series of solvents of different polarity starting from petroleum ether, ethyl acetate and methanol. The finding showed that the high antioxidant of *H. corymbosa* might be due the presence of bioactive compounds presence in the extract. Therefore, an extensive study on structure elucidation of compound is needed to determine the structure-activity relationship of the isolated compounds. Some of antioxidant activity and total phenolic content of this plant genus is summarized in Table 3 below.

Table 3: Antioxidant and phenolic contents of *Hedyotis-Oldenlandia* sp

Hedyotis-Oldenlandia sp.	Objectives	Extraction conditions			Outcomes	References
		State of input materials	Solid to solvent ratio	Solvent used		
H. diffusa	Antioxidant properties Therapeutic potential on gynaecological disease	Dried form of *H. diffusa*	20 g of dried *H. diffusa* were added into 100 ml of distilled water	Distilled water	The lag phase duration (min) of copper-induced low-density lipoprotein cholesterol oxidation of *H. diffusa* from 19.06 ± 0.11 to 35.70 ± 3.48	Ji et al. (2017)
H. biflora	*In vitro* α-glucosidase inhibition and antioxidant activity of hexane, ethyl acetate and methanol of *H. biflora*	Dried and Powdered form of *H. biflora*	1 kg of *H. biflora* was extracted with 3L solvent.	Hexane, ethyl acetate and methanol	The methanol extract of *H. biflora* showed potent effect compared to hexane and ethyl acetate extract. The 50% α-glucosidase inhibition of methanol extract was at the concentration of 480.20 ± 2.37 μg/ml.	Christhudas et al. (2013)
H. corymbosa	Optimisation of enzyme-assisted extraction, purification, antioxidant, characterization and its bioactives of polysaccharides from *Hedyotis corymbosa*	Dried form of *H. corymbosa*	-	Mixed solvent	DPPH radical scavenging capacity (82.23%) compared to Trolox (92.07%)	Lin et al. (2018)
H. corymbosa	Antioxidant evaluation of *H. corymbosa* extract	The aerial parts of *H. corymbosa* extract	-	Methanol	The total phenolic content in the methanolic extract of aerial parts was found to be 210 mg of gallic acid equivalents (GAE) in 100 g fresh weight basis	Sasikumar et al. (2010)
O. diffusa	Preparing the amino-modified active carbon cartridges for quercetin extraction	Powdered form of *O. diffusa*	*O. diffusa* powder brought from Incheon, Korea. 2 g of *O. diffusa* powder were dissolved in 0.03 L of solvent.	Chloroform, ethanol, water and methanol	Methanol was the best solvent for extracting *O. diffusa*	Zhu & Row (2011)

Structure-activity relationship (SAR) **of compounds**

Theoretical models that can be used to predict the physicochemical, biological and environmental properties of substances, or so called the relationship of chemical structure to biological activity are based on the qualitative method, structure–activity relationships (SARs) and quantitative structure–activity relationships (QSARs) (Mohapatra, 2020). The application of SAR and QSAR in revealing the nature of antioxidant has enable the researchers to design new and more efficient antioxidants for its therapeutic potential (Amic et al. 2007). For example, SAR can be explain by investigating the three key factors separately: mutual position of hydroxyl groups, their methylation, and the distance between phenyl and carboxylic group (Spiegel et al. 2020). Meanwhile, QSAR related to software tools used in the absence of available data for prioritization, classification, and screening level risk assessment (Pittinger et al. 2009).

A preliminary review on structure-activity relationship (SAR) of compounds in *Hedyotis-Oldenlandia* was undertaken by Lajis and Ahmad in 2006. This report is clearly described the highly divergent structural features intra-genus and its biological significance of the compounds isolated. Several attempts have been made to revise the molecular formula and structure accordingly with the finding conducted. In a report by Purushothaman et al. (1981), auricularine was found differ from borroreverine in its molecular formula due to its extra N-dimethyl group in the form of a N-Me amino group. Besides, D_2O-exchangeable proton was also not found unavailable in auricularine, compared to boverrine (Purushothaman et al.1981).

The correlation between SAR and antioxidant effect have also been reported during these years (Chen et al. 2016; Lajis and Ahmad, 2006). Further research on the bioactive constituents of *Hedyotis diffusa* Willd., has led to the isolation of a new acyl flavonol di-glycoside which was then characterized as kaempferol 3-O[2''-O-(E-6'''-O-feruloyl)-β-D-glucopyranosyl]-β-D-galactopyranoside by spectral and chemical methods from the methanolic extract. In addition, three known flavonol glycosides and six known iridoid glycosides were also being isolated successfully from this crude extract. The above-mentioned glycosides were tested for antioxidant effects on xanthine oxidase inhibition, xanthine-xanthine oxidase cytochrome c and TBA-MDA systems. It is noted that the antioxidant effect of *H. diffusa* was contributed by the presence of these flavonoid and iridoid compounds.

Five flavonol glycosides (kaempferol-3-O-[2-O-(6-O-E-feruloyl)-β-D-glucopyranosyl]-β-D-galactopyranoside, quercetin-3-O-[2-O-(6-O-E-feruloyl)-β-D-glucopyranosyl]-β-D-galactopyranoside, quercetin-3-O-[2-O-(6-O-E-feruloyl)-β-D-glucopyranosyl]-β-D-glucopyranoside, kaempferol-3-O-(2-O-β-D-glucopyranosyl)-β-D-galactopyranoside and quercetin-3-O-(2-O-β-D-glucopyranosyl)- β-D-galactopyranoside) and four O-acylated iridoid glycosides (6-O-Z-p-methoxy cinnamoyl scandoside methyl ester, 6-O-E-p-methoxy cinnamoyl scandoside methyl ester, 6-O-Z-p-coumaroyl scandoside methyl ester and 6-O-E-p-coumaroyl scandoside methyl ester) isolated from *H. diffusa* exhibited a significant neuroprotective effect on L-glutamate-damaged rat cortical cells in the concentration from 0.1 to 10 µM; further, the structure–activity study proved di-OH in the B ring and an acyl substituent in flavonoids, a p-methoxy group in the aromatic ring and a trans double bond in the acyl moiety of acylated iridoid glycosides might be crucial for the biological response (Kim et al. 2019). Wu et al. 2009 also found the inhibitory effect of oleanolic acid (2 and 8 µg/mL) isolated from *H. diffusa* against ras-transformed fibroblasts on R6 cells, and this inhibition might cause normal cells to secrete an inhibitory factor against the transformed cells but did not require direct cell–cell contact.

H. diffusa had been reported to contain potential anticomplement activity from HD-PS-1 acid homologous polysaccharides compared to HD-PS-2 (CH_{50}: 0.456 ± 0.008 mg/mL, AP_{50}: 0.572 ± 0.010 mg/mL), attributed from its uronic acids in the structure where the interaction occurred at C3 and C4 from the cascade (Huo et al. 2020). Yet, both exhibited antioxidant activities by scavenging DPPH radicals.

Other than that, many Chinese herbs are known its potential in treating various cancers especially during chemotherapy stage to achieve additive or synergistic therapeutic effects due to its structure relative activity of bioactive ingredients contained in the herbs. This is reported by Hu et al. (2015) which isolated three novel cyclotides, which are akin to the anti-cancer effects and brief as Diffusa cyclotide 1 to 3 (DC3 the most cytotoxic) from leaves and roots of *H. diffusa.* This mini protein from against prostate cancer cells peptide neckbone cross-braced by three disulfide binds in a cysteine-knot arrangements of cysteine I-IV, II-

IV, III-VI (Sze et al. 2009).

Antibacterial and antifungal activities

In spite of the long traditional uses of microbial origin antimicrobial molecules, plant bioactives have gained more interest lastly as high potential source of antimicrobial molecules (Gomaa et al. 2019; Belfarhi et al. 2020). This based on the continued increased resistance of different classes of microbes against the current known microbial based antibiotics (Srivastava et al. 2020). Compared to other medicinal plans, little information has been published so far about the antimicrobial activities of this species. However, early study reported the potential antibacterial activities of methanolic extracts of some *Hedyotis* species (Ahmad et al. 2005). They reported that species like *H. dichotoma* exhibited moderate activity against Gram-positive bacteria *Bacillus subtilis*, and methicillin-resistant *Staphylococcus aureus* (MRSA) and potent antimicrobial activities against the Gram-negative bacteria *Pseudomonas aeruginosa.*

Other species such as *Oldenlandia umbellata* showed also significant activity against *S. aureus* and *Escherichia coli*. The antibacterial activity was attributed to the presence of 1,2-dihydroxy anthraquinone (Alizarin) which was present in all antimicrobial bioactive fractions (Ahmad et al. 2005). Other study reported also that methanolic extract of *Oldenlandia corymbosa* methanolic extract have potent wide spectrum antimicrobial activities against Gram positive and Gram-negative bacteria such as (*Bacillus sp., Escherichia coli, Klebsiella sp., Proteus sp., Pseudomonas sp.,* and *Staphylococcus aureus*) with very low antifungal activity against *Candida albicans* (Hussain and Kumaresan, 2013; Das et al. 2019).

Recent study showed that the antimicrobial properties of the ethanol extract of *O. corymbosa* is attributed to the presence of fatty acid derivatives (Archana et al. 2020). However, in addition to the direct antimicrobial activities of some of *Oldenlandia* sp., recent study showed also that *O. umbellata* have been effectively used in the biosynthesis of silver nanoparticle of wide spectrum antimicrobial activities. The produced nanoparticles were highly compatible with human lung fibroblast cell line and exhibited potent activity against *Streptococcus mutans*, *Pseudomonas aeruginoas* and *Escherichia coli* (Subramanian et al. 2019).

Cytotoxic and other bioactivities

According to National Cancer dictionary, cytotoxic agent is defining as a substance that can kill cell including cell cancer. These compounds may stop cell from growing or can reduce the size of tumor cells. Many studies have reported the potential of *Hedyotis* plant species as antitumor agent to inhibit the tumor cell proliferation, migration, metastasis and invasion before becoming worst. The mechanism how the compound work could be by modifying the growth-related signalling pathway of tumor cell, cell immunity, and related to antioxidant activity (Han et al. 2020).

In 2017, Wang et al. has showed through in vitro assays study that *Hedyotis diffusa* Willd collected from China, Guangdong province was identified new active compounds which is three iridoid glycosides compounds and one new cerebroside. The compounds have high and moderate cytotoxic activity to seven human's malignant tumor cell lines known as human colon cancer cell HCT15, human lung cancer cell A459, human leukemia cell HL-60, human gastric gland carcinoma BCG-823, human nasopharyngeal cancer cell CNE-2, human prostate cancer cell PC-3 and human hepatoma cell (HepG2). The cytotoxic value of these compounds is reported between IC_{50} 9.6 µM to 89.3 µM.

In 2014, Dong et al. has reported that iridoid, stigmasterol, anthraquinones and glucosides compound from *Hedyotis diffusa* has potential in human breast cancer cell line MCF7 but should be avoid the intake with other chemotherapy drugs because it will reduce the efficacy of chemotherapy treatment. Quercetin and coumarin compound as predicted using network pharmacology approach by Liu et al. (2018), has potential to treat gastric cancer with potential mechanism through synergetic modulation on cell cycle, proliferation, invasion, migration, angiogenesis, apoptosis and differentiation. Hu et al. (2015) has found three novel cyclotides named as DC1 to DC3 showed cytotoxic activity with IC_{50} values between 1µM to 10 µM that can induce apoptosis, inhibit proliferation and inhibit migration of prostate cancer cells. The same plant species has studied by Zhang et al. (2016) found one anthraquinone compound and 13 flavonoids compounds that can inhibit the migration of ovarian cancer cells and induce the apoptosis activity.

Table 4: List of compounds with their activity towards specific targeting cells

***Hedyotis-Oldenlandia* sp.**	**Compounds**	**Target cell/ Activity**	**References**
Hedyotis diffusa Willd	iridoid glycosides, cerebrosides	Cell line of human colon cancer (HCT15), Human lung cancer (A459), Human leukemia (HL-60), Human gastric gland carcinoma (BCG-823), Human nasopharyngeal cancer (CNE-2), human prostate cancer (PC-3) and human hepatoma HepG2	Wang et al. 2017
	whole herb extract	Lung cancer	Gupta et al. 2004
	anthraquinones, iridoid glucosides and stigmasterols	Human breast cancer cell line (MCF7)	Dong et al. 2014
	aqueous plant extract	Colorectal cancer (CRC) cells	Lu et al. 2016
	whole plant water extract	Liver cancer (HepG2)	Chen et al. 2012
	13 flavonoids and 1 anthraquinone	Ovarian cancer cell (A2780)	Zhang et al. 2016
	quercetin and coumarin	Gastric cancer	Liu et al. 2018
	cyclotides DC1- DC3 (active peptide)	Prostate cancer	Hu et al. 2015
Hedyotis caudatifolia	hedyanthraquinones A and B	Tumor cell lines - acute promyelocytic leukemia cell (HL-60), human breast cancer cell (BCaP37) and human hepatic carcinoma cell (SMMC7721)	Jing et al. 2019
Hedyotis corymbosa	polysaccharide fraction	Murine Macrophage cell line (RAW264.7)	Lin et al. 2018
Hedyotis leschenaultiana	whole plant extract	Diabetic control	Sornalakshmi et al. 2016
H. capitellata, H. verticillate, H. dichotomo, H. pinifolia, H. corymbose, H. nudicaulis and *H. herbacea*	plant extract	Human T-lymphoblastics leukimia (CEM-SS) cell line	Lajis and Ahmad, 2006
Hedyotis puberula	leaf extract	Eggs, larvae and adults of *Anopheles stephensi*, *Aedes aegypti* and *Culex quinquefasciatus*	Azarudeen et al. 2016)

Another finding from Lu et al. (2016), a study using the whole extract of *Hedyotis diffusa* is effectively showed cytotoxic activity by apoptosis and anti-proliferative activities against human colorectal cancer (CRC) cell lines, inhibition of proliferation of liver cancer HepG2 and increase apoptosis in lung cancer cell (Chen et al. 2012; Gupta et al. 2004).

Another investigation by Jing et al. (2019) on *Hedyotis caudatifolia* has led to the isolation of two new compounds namely Hedyanthraquinones A and B. Hedyanthraquinones A possessed the ability to inhibit the growth of breast cancer cell BCaP37, hepatic carcinoma cell SMMC7721 and acute promyelocytic leukemia cell HL-60 with IC_{50} values of 26.29, 21.16 and 13.71 µM, respectively. Meanwhile, hedyanthraquinones B is potential in inhibiting HL-60 cell lines with IC_{50} value of 18.23 µM.

Another species of *Hedyotis corymbosa* was collected from natural herbal market in Gao Qiao, ChangSha China and revealed the anti-inflammatory activity of acid polysaccharides from the plant through reduction of the IL-1β, TNF-α and NO concentrations on murine RAW264.7 macrophage cells (Lin et al. 2018). This helps in preventing the development of tumor and cancer cells by controlling the chronic inflammation process (Han et al. 2020). In 2016, Sornalakshmi and the team has demonstrated of ethanol extract of *Hedyotis leschenaultiana* essential in diabetic control by reducing blood glucose level due to the whole plant extract consist of streroids, saponins, tannins, glycosides, flavonoids and phenols (Somalakshmi et al. 2016). Meanwhile, Seven *Hedyotis* plants species including *Hedyotis verticillata* were collected from Peninsular Malaysia by Ahmad et al. in 2005, where the species involved were *H. capitellata, H. verticillata, H. dichotomo, H. pinifolia, H. corymbose, H. nudicaulis* and *H. herbacea.* The extract undergoes cytotoxic test using MTT assay against human T-lymphoblastics leukimia (CEM-SS) cell line and showed low cytotoxic activity with CD_{50} value range from 21 to 41 g/ml. This finding indicates that *H. verticillata* also have similar toxicity effect as comparable as other species, but further investigation focusing on these species is needed to get scientific data.

A study conducted by Azarudeen et al. (2016) has reported different application view of the plant extract. Despite its beneficial uses to human being, the extract was found to be effective in mosquitocidal activity. The study displayed a significant effect on mortality of eggs, larvae and adults of *Anopheles stephensi, Aedes aegypti* and *Culex quinquefasciatus* after treated with *Hedyotis puberula* leave extract. In addition to its toxicity effect on human cell lines, this extract was also found to be effective to be used as biopesticide in replace to chemical insecticides available in current market. This finding has opened a new perspective in the development of natural mosquito control products in the future.

CONCLUSION

Nowadays, *Hedyotis-Oldenlandia* plant genus has still made into various preparations including pills and capsule in combination with other TCMs to ease digestive problem, suffering from diuretic, gastritis problem and pelvic inflammatory problem, which is a prolongation of the traditional uses of this plant. Based on this review, an extensive pharmacological study on *Hedyotis-Oldenlandia* sp. have been conducted in cell and animal experiments since years. Therefore, as an ethnomedicine widely used in China, further deep studies need to be carried out related to mechanisms of action for compounds or extracts existing in the plant species against certain target protein molecules. This will help in further elaborate and emphasize the pharmacological uses of the isolated compounds or standard extract of the plant in future

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEGEMENT

Authors would like also to thank Institute of Bioproduct Development (IBD) and Research Management Center at UTM, Malaysia, and Ese Wood Sdn. Bhd. for partial support through grant No. R.J130000.7609.4C367..

AUTHOR CONTRIBUTIONS

SN, MY, SZH, IMY, SHMS, RAM, MFM, HEE involved in data collection, writing the manuscript and designed the work. EK, LHH, HEE reviewed the manuscript. All authors read and approved the final version.

REFERENCES

Ahmad R, Ali AM, Israf DA, Ismail NH, Shaari K, Lajis NH. 2005. Antioxidant, radical-scavenging, anti-inflammatory, cytotoxic and antibacterial activities of methanolic extracts of some *Hedyotis* species. Life Sciences 76(17): 1953-1964.

Amic D, Davidovic-Amic D, Beslo D, Rastija V, Lucic B, Trinajstic N. 2007. SAR and QSAR of the antioxidant activity of flavonoids. Current medicinal chemistry 14(7): 827-845.

Anand U, Jacobo-Herrera N, Altemimi A, Lakhssassi N. 2019. A comprehensive review on medicinal plants as antimicrobial therapeutics: Potential avenues of biocompatible drug discovery. Metabolites 9(11): 258.

Archana V, Thomas NN, Rauf AA, Edwin BT. 2020. Fatty acid derivative of methanol extract of *Oldenlandia corymbosa*: A potential compound against *K. pneuminiae* and MCF-cell lines. International Journal for Research in Applied Sciences and Biotechnology. 7(3): 46-52.

Artanti N, Hanafi M, Andriyani R, Saraswaty V, Udin LZ, Lotulung PD, Fujita KI, Usuki Y. 2015. Isolation of an anti-cancer asperuloside from *Hedyotis corymbosa* L. Journal Trop Life Sci. 5: 88-91.

Azarudeen RM, Govindarajan M, Amsath A, Kadaikunnan S, Alharbi NS, Vijayan P, Muthukumaran U, Benelli G. 2016. Size-controlled fabrication of silver nanoparticles using the *Hedyotis puberula* leaf extract: toxicity on mosquito vectors and impact on biological control agents. RSC advances 6(99): 96573-96583.

Badr JM. 2008. Antioxidant and antimicrobial constituents of *Crucianella maritima* L. Natural Product Sciences 14(4): 227-232.

Behera SK, Rajasekaran C, Payas S, Fulzele DP, Doss CG, Siva R. 2018. In vitro flowering in *Oldenlandia umbellata* L. Journal of Ayurveda and integrative medicine. 9(2): 99-103.

Belfarhi L, Bouhenna MM, Bouafir Y, Boumehira AZ, Nebbak A, Ziani BEC, Bachari K, Dailin DJ, El Enshasy H. 2020. Therapeutic herbal tea: Medicinal properties and toxicology- A review. Bioscience Research 17: 793-814.

Brenda SK, Comini LR, Grasso S, Aguilar JJ, Marioni J, Marta SC, Montoya SC. 2012. Determination of non-toxic and subtoxic concentrations of potential antiviral natural anthraquinones. Lat. Am. J. Pharm 31(1): 51-56.

Chambial S, Dwivedi S, Shukla KK, John PJ, Sharma P. 2013. Vitamin C in disease prevention and cure: an overview. Indian Journal of Clinical Biochemistry 28(4): 314-328.

Chen R, He J, Tong X, Tang L, Liu M. 2016. The *Hedyotis diffusa* Willd. (Rubiaceae): a review on phytochemistry, pharmacology, quality control and pharmacokinetics. Molecules 21(6): 710.

Chen X, Zhu P, Liu B, Wei L, Xu Y. 2018. Simultaneous determination of fourteen compounds of *Hedyotis diffusa* Willd extract in rats by UHPLC–MS/MS method: application to pharmacokinetics and tissue distribution study. Journal of pharmaceutical and biomedical analysis 159: 490-512.

Chen XZ, Cao ZY, Chen TS, Zhang YQ, Liu ZZ, Su YT, Liao LM, Du J. 2012. Water extract of *Hedyotis diffusa* Willd suppresses proliferation of human HepG2 cells and potentiates the anticancer efficacy of low-dose 5-fluorouracil by inhibiting the CDK2-E2F1 pathway. Oncology reports 28(2): 742-748.

Chimkode R, Patil MB, Jalalpure S, Pasha TY. 2009. A Study of hepatoprotective activity of *Hedyotis corymbosa*. Linn, in albino rats. Ancient science of life 28(4): 32.

Chopra RN, Nayar SL, Chopra IC. 1986. Glossary of Indian medicinal plants (including the supplement), Council Sci. Ind. Res., New Delhi, India. 1986.

Christhudas IN, Kumar PP, Sunil C, Vajravijayan S, Sundaram RL, Siril SJ, Agastian P. 2013. In vitro studies on α-glucosidase inhibition, antioxidant and free radical scavenging activities of *Hedyotis biflora* L. Food chemistry 138(2-3): 1689-1695.

Chua LS. 2013. A review on plant-based rutin extraction methods and its pharmacological activities. Journal of ethnopharmacology 150(3): 805-817.

Conrad J, Vogler B, Klaiber I, Reeb S, Guse JH, Roos G, Kraus W. 2001. Vanillic acid 4-O-β-d-(6′-O-galloyl) glucopyranoside and other constituents from the bark of *Terminalia* *macroptera* Guill. et Perr. Natural product letters 15(1): 35-42.

Dall'Acqua S, Cervellati R, Speroni E, Costa S, Guerra MC, Stella L, Greco E, Innocenti G. 2009. Phytochemical composition and antioxidant activity of *Laurus nobilis* L. leaf infusion. Journal of Medicinal Food 12(4): 869-876.

Das S, Mondal N, Mondal S, Ghosh P, Ghosh C, Das C, Chatterjee S. 2019. Botanical features, phytochemical and pharmacological overviews of *Oldenlandia corymbosa* Linn.: A brief review. The Pharma Innovation Journal 8(2): 464-468.

Das, K. G., & Bharali, R. 2020. In vitro evaluation of antioxidant activities of *Oldenladia corymbosa* L. (syn. *Hedyotis corymbosa*) fractionated extracts in various solvent. International Journal of Pharmaceutical Sciences and Research 11(6): 2840-2850.

De Zoysa HK, Herath PN, Cooper R, Waisundara VY. 2017. Paspanguwa herbal formula, a traditional medicine of Sri Lanka: A critical review. Journal of Complementary Medicine and Alternative Healthcare 3(2): 1-8.

Dey A, De JN. 2012. Traditional use of plants against snakebite in Indian subcontinent: a review of the recent literature. African Journal of Traditional, Complementary and Alternative Medicines 9(1): 153-174.

do Nascimento JE, de Morais SM, de Lisboa DS, de Oliveira Sousa M, Santos SA, Magalhães FE, Campos AR. 2018. The orofacial antinociceptive effect of Kaempferol-3-O-rutinoside, isolated from the plant *Ouratea fieldingiana*, on adult zebrafish (Danio rerio). Biomedicine & Pharmacotherapy 107: 1030-1036.

Dong Q, Ling B, Gao B, Maley J, Sammynaiken R, Yang J. 2014. *Hedyotis diffusa* water extract diminished the cytotoxic effects of chemotherapy drugs against human breast cancer MCF7 cells. Natural product communications 9(5):1934578X1400900529.

Endrini, S. 2011. Antioxidant activity and anticarcinogenic property of 'rumput mutiara' *Hedyotis corymbosa* (L.) Lam and *Pilea trinervia* (Roxb.) Wight. Journal of Medicinal Plants Research 5(16): 3715-3718.

Félix-Silva J, Silva-Junior AA, Zucolotto SM, Fernandes-Pedrosa MD. 2017. Medicinal plants for the treatment of local tissue damage induced by snake venoms: an overview from traditional use to pharmacological evidence. Evidence-Based Complementary and Alternative Medicine. 2017. Article ID 5748256.

Ghosh S, Datta P, Saha K, Sarkar A, Muhuri DC, Gomes A, Gomes A. 2015. Herbs and herbal constituents active against arthritis. SAJ Pharmacy and Pharmacology 2(1): 1-3.

Gille A, Bodor ET, Ahmed K, Offermanns S. 2008. Nicotinic acid: pharmacological effects and mechanisms of action. Annu. Rev. Pharmacol. Toxicol. 48: 79-106.

Gohari AR, Ostad SN, Moradi-Afrapoli F, Malmir M, Tavajohi S, Akbari H, Saeidnia S. 2012. Evaluation of the cytotoxicity of *Satureja spicigera* and its main compounds. The Scientific World Journal. 2012. Article ID 203861

Gomaa SE, Yahayu M, Nurjayadi M, Dailin DJ, El Enshasy H. 2019. Antimicrobial compounds from *Catharanthus roseus* -A Review. International Journal of Science and Technology Research. 8: 113-121.

Guo X, Wang RJ, Simmons MP, But PP, Yu J. 2013. Phylogeny of the Asian *Hedyotis–Oldenlandia* complex (Spermacoceae, Rubiaceae): Evidence for high levels of polyphyly and the parallel evolution of diplophragmous capsules. Molecular phylogenetics and evolution 67(1): 110-122.

Gupta S, Zhang D, Yi J, Shao J. 2004. Anticancer activities of *Oldenlandia diffusa*. Journal of Herbal Pharmacotherapy 4(1): 21-33.

Hamzah AS, Lajis NH. 1998. Chemical constituents of *Hedyotis herbacea*. ASEAN Rev Biodivers Environ Conserv 2: 1-6.

Hamzah AS, Lajis NH, Sargent MV. 1994. Kaempferitrin from the leaves of *Hedyotis verticillata* and its biological activity. Planta Medica 60(04):388-389.

Han X, Zhang X, Wang Q, Wang L, Yu S. 2020. Antitumor potential of *Hedyotis diffusa* Willd: A systematic review of bioactive constituents and underlying molecular mechanisms. Biomedicine & Pharmacotherapy 130: 110735.

He J, Li J, Liu H, Yang Z, Zhou F, Wei T, Dong Y, Xue H, Tang L, Liu M. 2018a. Scandoside exerts anti-Inflammatory effect via suppressing NF-κB and MAPK signaling pathways in LPS-induced RAW 264.7 macrophages. International Journal of Molecular Sciences 19(2): 457.

He J, Lu X, Wei T, Dong Y, Cai Z, Tang L, Liu M. 2018b. Asperuloside and asperulosidic acid exert an anti-inflammatory effect via suppression of the NF-κB and MAPK signaling pathways in LPS-induced RAW 264.7 macrophages. International Journal of Molecular Sciences 19(7): 2027.

Hejazi II, Beg MA, Imam A, Athar F, Islam A. 2021. Glossary of phytoconstituents: Can these be repurposed against SARS CoV-2. A quick in silico screening of various phytoconstituents from plant *Glycyrrhiza glabra* with SARS CoV-2 main protease. Food and Chemical Toxicology. 150:112057.

Hema V, Vasudev A, Rani AP. 2009. Phytochemical screening of *Oldenlandia umbellate*. International Journal of Chemical Sciences 7(3): 2096-2102.

Hsu HY, Tsai LH. 2000. The investigation of oleanolic acid and ursolic acid combined with high dose ionizing radiation on the apoptosis of HL-60 cells. Cancer Detect. PreV. 24: 89.

Hu E, Wang D, Chen J, Tao X. 2015. Novel cyclotides from *Hedyotis diffusa* induce apoptosis and inhibit proliferation and migration of prostate cancer cells. International Journal of Clinical and Experimental Medicine 8(3): 4059.

Huo J, Lu Y, Jiao Y, Chen D. 2020. Structural characterization and anticomplement activity of an acidic polysaccharide from *Hedyotis diffusa*. International Journal of Biological Macromolecules 155: 1553-1560.

Hussain AZ, Kumaresan S. 2013. Phytochemical and antimicrobial evaluation of *Oldenlandia corymbosa*. Asian Journal of Plant Science and Research 3(4): 155-158.

Iqbal J, Abbasi BA, Mahmood T, Kanwal S, Ali B, Shah SA, Khalil AT. 2017. Plant-derived anticancer agents: A green anticancer approach. Asian Pacific Journal of Tropical Biomedicine 7(12): 1129-1150.

Jang YS, Wang Z, Lee JM, Lee JY, Lim SS. 2016. Screening of Korean natural products for anti-adipogenesis properties and isolation of kaempferol-3-O-rutinoside as a potent anti-adipogenetic compound from *Solidago virgaurea*. Molecules 21(2): 226.

Ji S, Fattahi A, Raffel N, Hoffmann I, Beckmann MW, Dittrich R, Schrauder M. 2017. Antioxidant effect of aqueous extract of four plants with therapeutic potential on gynecological diseases; *Semen persicae, Leonurus cardiaca, Hedyotis diffusa*, and *Curcuma zedoaria*. European Journal of Medical Research 22(1): 1-8.

Jiang S, Zhang HJ, Wang KW. 2021. Iridoids and Triterpenoid Constituents of *Hedyotis assimilis*. Chemistry of Natural Compounds 57(1): 183-186.

Jing Y, Zhang HJ, Wang KW, Wang XX, Chen ML, Wang H, Wu B. 2019. Two novel anthraquinones with cytotoxicity from *Hedyotis caudatifolia*. Phytochemistry Letters 29: 134-137.

Kadir MF, Karmoker JR, Alam MD, Jahan SR, Mahbub S, Mia MM. 2015. Ethnopharmacological survey of medicinal plants used by traditional healers and indigenous people in Chittagong Hill Tracts, Bangladesh, for the treatment of snakebite. Evidence-Based Complementary and Alternative Medicine. 2015. Article ID 871675

Khan S, Riaz N, Afza N, Malik A, Aziz-ur-Rehman, Iqbal L, Lateef M. 2009. Antioxidant constituents from *Cotoneaster racemiflora*. Journal of Asian Natural Products Research 11(1): 44-48.

Khan T, Ali M, Khan A, Nisar P, Jan SA, Afridi S, Shinwari ZK. 2020. Anticancer plants: A review of the active phytochemicals, applications in animal models, and regulatory aspects. Biomolecules 10(1): 47.

Khettal B, Kadri N, Tighilet K, Adjebli A, Dahmoune F, Maiza-Benabdeslam F. 2017. Phenolic compounds from *Citrus* leaves: Antioxidant activity and enzymatic browning inhibition. Journal of Complementary and Integrative Medicine 14(1). 20160030.

Khlifi R, Dhaouefi Z, Toumia IB, Lahmar A, Sioud F, Bouhajeb R, Bellalah A, Chekir-Ghedira L. 2020. *Erica multiflora* extract rich in quercetin-3-O-glucoside and kaempferol-3-O-glucoside alleviates high fat and fructose diet-induced fatty liver disease by modulating metabolic and inflammatory pathways in Wistar rats. The Journal of Nutritional Biochemistry 86: 108490.

Kim JH, Kim M, Kim JM, Lee MK, Seo SJ, Park KY. 2019. Afzelin suppresses proinflammatory responses in particulate matter-exposed human keratinocytes. International Journal of Molecular Medicine 43(6): 2516-2522.

Kim TP, Mai TP, Phi PN. 2015. Two new compounds from *Hedyotis lindleyana*. Natural product communications 10(7):1934578X1501000701.

Kumar N, Goel N. 2019. Phenolic acids: Natural versatile molecules with promising therapeutic applications. Biotechnology Reports. 2019 Dec 1;24:e00370.

Lajis NH, Ahmad R. 2006. Phytochemical studies and pharmacological activities of plants in genus *Hedyotis/ Oldenlandia*. In Studies in Natural Products Chemistry 33: 1057-1090.

Lakshmana Raju B, Lin SJ, Hou WC, Lai ZY, Liu PC, Hsu FL. 2004. Antioxidant iridoid glucosides from *Wendlandia formosana*. Natural Product Research 18(4): 357-364.

Lee SY, So YJ, Shin MS, Cho JY, Lee J. 2014. Antibacterial effects of afzelin isolated from *Cornus macrophylla* on *Pseudomonas aeruginosa*, a leading cause of illness in immunocompromised individuals. Molecules 9(3): 3173-3180.

Li H, Lai Z, Yang H, Peng J, Chen Y, Lin J. 2019. *Hedyotis diffusa* Willd. inhibits VEGF-C-mediated lymphangiogenesis in colorectal cancer via multiple signalling pathways. Oncology Reports 42(3): 1225-1236.

Liang Z, He M, Fong W, Jiang Z, Zhao Z. 2008. A comparable, chemical and pharmacological analysis of the traditional Chinese medicinal herbs *Oldenlandia diffusa* and *O. corymbosa* and a new valuation of their biological potential. Phytomedicine 15(4): 259-267.

Lin D, Xiao M, Zhao J, Li Z, Xing B, Li X, Kong M, Li L, Zhang Q, Liu Y, Chen H. 2016. An overview of plant phenolic compounds and their importance in human nutrition and management of type 2 diabetes. Molecules 21(10): 1374.

Lin LM, Xiong SH, Zhao LJ, Tang J, Zhang ZM, Li YM, Zheng T, Xia BH. 2018. Extraction, characterization, antioxidant, and immunostimulatory activities of polysaccharides from *Hedyotis corymbosa*. Evidence-Based Complementary and Alternative Medicine. 2018. Article ID 7802639

Liu X, Wu J, Zhang D, Wang K, Duan X, Meng Z, Zhang X. 2018. Network pharmacology-based approach to investigate the mechanisms of *Hedyotis diffusa* Willd. in the treatment of gastric cancer. Evidence-Based Complementary and Alternative Medicine. 2018.

Lu PH, Chen MB, Ji C, Li WT, Wei MX, Wu MH. 2016. Aqueous *Oldenlandia diffusa* extracts inhibits colorectal cancer cells via activating AMP-activated protein kinase signalings. Oncotarget 7(29): 45889.

Mahibalan S, Rao PC, Khan R, Basha A, Siddareddy R, Masubuti H, Fujimoto Y, Begum AS. 2016. Cytotoxic constituents of *Oldenlandia umbellata* and isolation of a new symmetrical coumarin dimer. Medicinal Chemistry Research 25(3): 466-472.

Mohapatra A. 2020. Software tools for toxicology and risk assessment. In Information Resources in Toxicology (pp. 791-812). Academic Press.

Mohotti S, Rajendran S, Muhammad T, Strömstedt AA, Adhikari A, Burman R, de Silva ED, Göransson U, Hettiarachchi CM, Gunasekera S. 2020. Screening for bioactive secondary metabolites in Sri Lankan medicinal plants by microfractionation and targeted isolation of antimicrobial flavonoids from *Derris scandens*. Journal of Ethnopharmacology 246: 112158.

Moroh JL, Fleury Y, Coulibaly A, Labia R, Leguérinel I. 2019. Chemo-Diversity of Antibacterial anthraquinones from the roots of *Morinda morindoides*. The Natural Products Journal 9(4): 256-261.

National Institutes of Health. National Cancer Institute Dictionary of Cancer Terms.

Neupane S, Dessein S, Wikström N, Lewis PO, Long C, Bremer B, Motley TJ. 2015. The *Hedyotis-Oldenlandia* complex (Rubiaceae: Spermacoceae) in Asia and the Pacific: Phylogeny revisited with new generic delimitations. Taxon 64(2): 299-322.

Nguyen GK, Zhang S, Wang W, Wong CT, Nguyen NT, Tam JP. 2011. Discovery of a linear cyclotide from the bracelet subfamily and its disulfide mapping by top-down mass spectrometry. Journal of Biological Chemistry 286(52): 44833-44844.

Nguyen HA, Khieu TT, Van Nguyen T, Dao TD, Tran QD, Nguyen TT, Nguyen BC, Trinh TT, Van Tran S. 2018. Chemical constituents of *Hedyotis pinifolia* Wall. collected in Thua Thien Hue. Vietnam Journal of Science and Technology 56(4): 446.

Obana A, Gohto Y, Nakazawa R, Moriyama T, Gellermann W, Bernstein PS. 2020. Effect of an antioxidant supplement containing high dose lutein and zeaxanthin on macular pigment and skin carotenoid levels. Scientific Reports 10(1): 1-2.

Ong HC, Zuki RM, Milow P. 2011. Traditional knowledge of medicinal plants among the Malay villagers in Kampung Mak Kemas, Terengganu, Malaysia. Studies on Ethno-medicine 5(3): 175-185.

Ozawa Y, Sasaki M. 2013. Diabetes: Chapter 23. Lutein and Oxidative Stress-Mediated Retinal Neurodegeneration in Diabetes. Elsevier Inc. Chapters; 2013 Oct 29.

Pan SY, Litscher G, Gao SH, Zhou SF, Yu ZL, Chen HQ, Zhang SF, Tang MK, Sun JN, Ko KM. 2014. Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources. Evidence-Based Complementary and Alternative Medicine. 2014, Article ID 525340.

Permana D. 2002. Phytochemical and Biological Activity Studies of *Hedyotis herbacea*, *Hedyotis diffusa* and roots of *Garcinia atroviridis* (Doctoral dissertation, Universiti Putra Malaysia).

Phuyal N, Jha PK, Raturi PP, Rajbhandary S. 2020. Total phenolic, flavonoid contents, and antioxidant activities of fruit, seed, and bark extracts of *Zanthoxylum armatum* DC. The Scientific World Journal. 2020, Article ID 8780704.

Pittinger, C., and Mohapatra, A. 2009. Chapter 69 - Software Tools for Toxicology and Risk Assessment. In Information Resources in Toxicology 2009 (P. Wexler, S. G. Gilbert, P. J. Hakkinen and A. Mohapatra, eds.) (pp. 631-638). Academic Press.

Purushothaman KK, Sarada A. 1981. Structure of auricularine, a bis-indole alkaloid from *Hedyotis auricularia*. Phytochemistry. 20(2): 351-352.

Quattrocchi U. 2012. CRC world dictionary of medicinal and poisonous plants: common names, scientific names, eponyms, synonyms, and etymology (5 Volume Set). CRC press; 2012 May 3.

Ramamoorthy S, Mudgal G, Rajesh D, Nawaz Khan F, Vijayakumar V, Rajasekaran C. 2009. Characterisation of novel pH indicator of natural dye *Oldenlandia umbellata* L. Natural Product Research 23(13): 1210-1217.

Rekha S, Srinivasan V, Vasanth S, Gopal RH. 2006. The in vitro antibacterial activity of *Hedyotis umbellata*. Indian Journal of Pharmaceutical Sciences 68(2): 236-238.

Sahu AK, Padhan AR, Sa N, Padhan AK. 2020. Phytochemical evaluation and in-vitro anthelmintic activity of *Oldenlandia corymbosa*. International Research Journal of Pharmaceutical and Biosciences 5(4): 1-13.

Sasikumar JM, Maheshu V, Aseervatham G, Darsini D. In vitro antioxidant activity of *Hedyotis corymbosa* (L.) Lam. aerial parts. Indian J Biochem Biophys 47(1): 49-52.

Shan M, Yu S, Yan H, Guo S, Xiao W, Wang Z, Zhang L, Ding A, Wu Q, Li SF. 2017. A review on the phytochemistry, pharmacology, pharmacokinetics and toxicology of geniposide, a natural product. Molecules 22(10): 1689.

Shao J, Gong G, Trombetta L. 2011. An evidence-based perspective of *Hedyotis diffusa* or *Oldenlandia diffusa* (spreading *Hedyotis*) for cancer patients. In Evidence-based Anticancer Materia Medica 2011 (pp. 179-192). Springer, Dordrecht.

Silva VC, Bolzani VD, Young M, Lopes MN. 2007. A new antifungal phenolic glycoside derivative, iridoids and lignans from *Alibertia sessilis* (vell.) k. schum. (Rubiaceae). Journal of the Brazilian Chemical Society 18(7): 1405-1409.

Sivapraksam SS, Karunakaran K, Subburaya U, Kuppusamy S, Subashini TS. 2014. A review on phytochemical and pharmacological profile of *Hedyotis corymbosa* Linn. Int J Pharm Sci Rev Res 26: 320-324.

Song Y, Wang H, Pan Y, Liu T. 2019. Investigating the multi-target pharmacological mechanism of *Hedyotis diffusa* Willd acting on prostate Cancer: a network pharmacology approach. Biomolecules 9(10): 591.

Sornalakshmi V, Tresina Soris P, Paulpriya K, Packia Lincy M, Mohan VR. 2016. Oral glucose tolerance test (OGTT) in normal control and glucose induced hyperglycemic rats with *Hedyotis leschenaultiana* DC. Group. 1: 1-9.

Spiegel M, Kapusta K, Kołodziejczyk W, Saloni J, Żbikowska B, Hill GA, Sroka Z. 2020. Antioxidant activity of selected phenolic acids–ferric reducing antioxidant power assay and QSAR analysis of the structural features. Molecules 25(13): 3088.

Srivastava S, Dashora K, Ameta KL, Singh NP, El-Enshasy HA, Pagano MC, Hesham AE, Sharma GD, Sharma M, Bhargava A. 2021. Cysteine-rich antimicrobial peptides from plants: The future of antimicrobial therapy. Phytotherapy Research 35(1): 256-277.

Su Y, Bi JL, Wang YH, Tan Y, Yang J, Liu HX, Gu W, Yin GF, Long CL. 2012. Chemical constituents from *Chirita longgangensis* var. *hongyao* with inhibitory activity against porcine respiratory and reproductive syndrome virus. Journal of the Brazilian Chemical Society. 23(10): 1925-1932.

Subramanian P, Ravichandran A, Manoharan V, Muthukaruppan R, Somasundaram S, Pandi B, Krishnan A, Marimuthu PN, Somasundaram SS, You S. 2019. Synthesis of *Oldenlandia umbellata* stabilized silver nanoparticles and their antioxidant effect, antibacterial activity, and bio-compatibility using human lung fibroblast cell line WI-38. Process Biochemistry 86:196-204.

Suruse PB, Duragkar NJ, Deshpande SA. 2015. Evaluation of in vitro antimalarial activity of *Hedyotis herbacea* by Schizont Maturation Inhibition Assay. International Journal of Pharmaceutical and Phytopharmacological Research 4(6): 328-330.

Sze SK, Wang W, Meng W, Yuan R, Guo T, Zhu Y, Tam JP. 2009. Elucidating the structure of cyclotides by partial acid hydrolysis and LC−MS/MS analysis. Analytical Chemistry 81(3): 1079-1088.

Taiwo FO, Oyedeji O, Osundahunsi MT. 2019. Antimicrobial and antioxidant properties of kaempferol-3-O-glucoside and 1-(4-Hydroxyphenyl)-3-phenylpropan-1-one isolated from the leaves of *Annona muricata* (Linn.). Journal of Pharmaceutical Research International 29: 1-3.

Wang C, Zhou X, Wang Y, Wei D, Deng C, Xu X, Xin P, Sun S. 2017. The antitumor constituents from *Hedyotis diffusa* Willd. Molecules. 22(12): 2101.

Wang Y, Tang C, Zhang H. 2015. Hepatoprotective effects of kaempferol 3-O-rutinoside and kaempferol 3-O-glucoside from *Carthamus tinctorius* L. on CCl4-induced oxidative liver injury in mice. Journal of Food and Drug Analysis. 23(2): 310-317.

Wang Y, Wang C, Lin H, Liu Y, Li Y, Zhao Y, Li P, Liu J. 2018. Discovery of the potential biomarkers for discrimination between *Hedyotis diffusa* and *Hedyotis corymbosa* by UPLC-QTOF/MS Metabolome Analysis. Molecules 23(7): 1525.

Wu YB, Zheng CJ, Qin LP, Sun LN, Han T, Jiao L, Zhang QY, Wu JZ. 2009. Antiosteoporotic activity of anthraquinones from *Morinda officinalis* on osteoblasts and osteoclasts. Molecules 14(1): 573-583.

Xianyuan L, Wei Z, Yaqian D, Dan Z, Xueli T, Zhanglu D, Guanyi L, Lan T, Menghua L. 2019. Anti-renal fibrosis effect of asperulosidic acid via TGF-β1/smad2/smad3 and NF-κB signaling pathways in a rat model of unilateral ureteral obstruction. Phytomedicine. 53: 274-285.

Yang J, Guo J, Yuan J. 2008. In vitro antioxidant properties of rutin. LWT-Food Science and Technology. 41(6): 1060-1066.

Yousef, S., Rajagopal, P. L. & Hanima, M.V. 2018. Therapeutic Utility of *Oldenlandia corymbosa* Linn. Journal of International Academic Research for Multidisciplinary. 5(12).178-186.

Zhang L, Zhang J, Qi B, Jiang G, Liu J, Zhang P, Ma Y, Li W. 2016. The anti-tumor effect and bioactive phytochemicals of *Hedyotis diffusa* Willd on ovarian cancer cells. Journal of Ethnopharmacology 192: 132-139.

Zhang, X., Huang, H., Zhang, Q., Fan, F., Xu, C., Sun, C., Li, X. & Chen, K. 2015. Phytochemical characterization of Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) of 17 cultivars and their antioxidant properties. International Journal of Molecular Sciences 16(6): 12467-12481.

Zhang Y, Liang Y, He C. 2017. Anticancer activities and mechanisms of heat-clearing and detoxicating traditional Chinese herbal medicine. Chinese Medicine 12(1): 1-5.

Zhu T, Row KH. 2011. Preparation of amino-modified active carbon cartridges and their use in the extraction of quercetin from *Oldenlandia diffusa*. Journal of Pharmaceutical and Biomedical Analysis 56(4): 713-720.