THE PHARMACOLOGICAL POTENTIAL OF ASPIDINOL – A PROMISING PHYTOCONSTITUENT

Abstract

Phytoconstituents possess diverse biological activities including medicinal, therapeutic, and nutritional as well as play vital roles in the plant's growth, development, interactions with other organisms, defense against pathogens and to attract pollinators. Various groups of phytoconstituents, such as alkaloids, tannins, flavonoids, , glycosides, saponin,s terpenoids, lignans, and resins, are found in different plant species, demonstrating efficacy and potency in providing health benefits for humans and animals. Phytoconstituents have been integral to systems of traditional medicine for centuries, with many cultures relying on plant-derived products or compounds for treating various health conditions. Modern pharmacology and the pharmaceutical industry recognize their potential for developing novel drugs and dosage forms, as around 80% of the global population depends on natural products and traditional medicine for primary healthcare. Recent advancements in technology have facilitated the study of phytoconstituents, allowing for deeper insights into their mechanisms of action and applications in drug development, nutraceuticals, and herbal medicine, leading to innovative treatments and improved health outcomes. Several pharmaceuticals available in the market are derived from or inspired by phytoconstituents found in plants, such as paclitaxel, reserpine, berberine, vincristine, morphine, nicotine and aspirin. These phytoconstituents demonstrated various health benefits, including anti-inflammatory, anti-microbial, and cardiovascular effects in the studies. This chapter focuses on Aspidinol, a phloroglucinol found in certain plants, particularly in ferns (*Pteridophyte*) and some traditional medicinal herbs. It has demonstrated several potential medicinal

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properties, including anti-microbial, anti-parasitic, anti-malarial, and anti-cancer activities. Although promising, further research is needed to fully understand Aspidinol's mechanisms of action and practical implications in healthcare. The potential pharmacological applications of Aspidinol in healthcare make it an intriguing subject for further research and drug development. However, additional investigations are necessary to uncover its full therapeutic potential and mechanisms of action for its effective utilization in medicine**.**

Keywords: Phytoconstituents, Modern pharmacology, Cytotoxic activity, Parasitic infections, Drug development

I. INTRODUCTION

Phytoconstituents, naturally occurring chemical compounds are responsible for the various biological activities and properties of plants, including their medicinal, therapeutic, and nutritional potential. They are not only essential for the plant's growth and development but also play essential roles in interactions with other organisms, defense mechanisms against pathogens, and attracting pollinators [1]. Numerous types of phytoconstituents are found in different plant species, and they can be classified into several major groups e.g. alkaloids, flavonoids, tannins, glycosides, terpenoids, saponins, lignans and resins etc. [2]. Studies reported the efficacy and potency of phytoconstituents in health benefits for humans and animals [3]. Not only today but for years, Phytoconstituents have been an area of great interest to researchers and scientists due to their possible medicinal and therapeutic properties. Many pharmaceutical drugs are derived from plant products or compounds [4]. Natural products and their phytoconstituent-based formulations have been an integral part of traditional medicine systems (TMS) for centuries such as Ayurveda (India), Native American Herbal Medicine (United States), Traditional Chinese Medicine (China), Arabic Medicine (Middle East) and various herbal medicine systems in different cultures have long relied on the use of plant-derived compounds for treating various health conditions. These systems know the therapeutic properties of natural products and phytoconstituents and utilize them in herbal remedies and formulations to promote health and well-being [5,6,7]. Today, the modern pharmacology and pharmaceutical industries are recognizing the potential of phytoconstituents for the development of novel drugs and dosage forms due to the growing interest of the population in natural products and traditional medicine. Approximately 80% of the global population relies on natural products and traditional medicine for their primary healthcare needs, according to the World Health Organization (WHO) [8].

Nowadays, the study of phytoconstituents has become more accessible and efficient due to the availability of advanced modern methods and technology that provides the easy and elaborated investigation of the mechanisms of action, specific cellular targets, and biochemical pathways of these natural compounds with greater precision [9]. This deeper understanding allows for more effective utilization of phytoconstituents in various applications, such as the development of drugs, nutraceuticals, and herbal medicine, potentially leading to innovative treatments and improved health outcomes.

In modern drug development, researchers isolate and study specific phytoconstituents to understand their mechanisms of action and potential therapeutic applications [10]. Several pharmaceutical drugs available today in the market are derived from or inspired by phytoconstituents found in plants. For example, the anti-cancer drug paclitaxel is derived from the yew tree, and aspirin was initially developed from compounds found in willow bark [11]. Curcumin, a curcuminoid compound in *Curcuma longa* L., exhibits potent anti-oxidant and anti-inflammatory action and is being investigated for its potential benefits in conditions such as arthritis, cancer and cardiovascular diseases [12]. Quercetin, a flavonoid in fruits and vegetables, has anti-oxidant, anti-inflammatory, and anti-viral action and is explored for potential benefits in allergies, respiratory conditions, and cardiovascular health [13]. Resveratrol, a type of natural phenol present in red grapes and berries, demonstrates anti-oxidant and anti-inflammatory effects and is investigated for potential benefits in cardiovascular health, neuro-protection, and anti-aging [14]. Allicin, an organosulfur compound from the *Allium* genus, has anti-microbial and cardiovascular benefits and is studied for potential effects on lowering cholesterol levels and blood pressure. Capsaicin,

found in the genus Capsicum, has analgesic and anti-inflammatory properties, is used in topical creams for pain relief, and may offer potential benefits in weight management [15]. Reserpine is an alkaloid of the plant *Rauwolfia serpentina*. It has been used historically as an anti-hypertensive medication due to its ability to reduce blood pressure by depleting neurotransmitters like norepinephrine and serotonin. However, its use has diminished in modern medicine due to side effects and the availability of more effective antihypertensive drugs [16]. Glycyrrhizin, a triterpenoid saponin found in *Glycyrrhiza glabra* L. root, has anti-inflammatory, anti-viral, antioxidant and immunomodulatory properties. It is beneficial for respiratory issues, liver health, and allergies [17]. Vincristine, a natural alkaloid obtained from *Catharanthus roseus* L. is a key component of chemotherapy treatment for various cancers, particularly leukemia and lymphoma. It works by disrupting the formation of microtubules in dividing cells, inhibiting cell division and leading to cancer cell death [18]. Tinosporine, a furanolactone found in the *Tinospora cordifolia* (Willd.) Miers ex Hook.f. & Thomson, possesses immunomodulatory, anti-inflammatory and antioxidant properties. It is of interest in traditional medicine and research due to its potential role in enhancing the immune system and its possible benefits in various inflammatory and oxidative stress-related conditions [19]. Eugenol is a phenolic compound present in essential oils of *Syzygium aromaticum*. It exhibits anti-inflammatory, analgesic, and anti-microbial properties. It has been investigated for its potential role in pain relief, dental care and as an anti-microbial agent against several species of bacteria and fungi [20].

This chapter discusses a phytoconstituent named Aspidinol. Chemically, it is phloroglucinol that was first reported in *Aspidium felix-mas* f. chrysocarpon (Fée) Milde (male fern) in 1899 [21]. This chapter summarized the biological source (Table 1) and pharmacological aspects of Aspidinol. To write this chapter, information was exhausted from the online available literature like research papers and review articles. Results of this study indicate Aspidinol is a natural compound found in certain plants, particularly in *Pteridophytes* (ferns) and some traditional medicinal herbs. Studies suggest that Aspidinol displays potential medicinal properties, including anti-microbial, anti-parasite, anti-malarial, and anti-cancer activities. Its promising pharmacological activities make it an intriguing subject for further research and potential application in the development of new drugs and therapeutic agents. Nevertheless, more research is needed to fully understand the compound's mechanisms of action and its practical implications in healthcare.

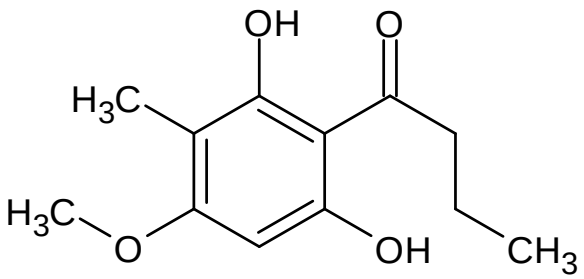

Figure 1: Structure of Aspidinol (2,6-Dihydroxy-4-methoxy-3-methylbutyrophenone) [21, 29]

Table 1: Plants Source of Aspidinol.

Sl no.	Biological Source	Plant part	Reference
1.	Athyrium multidentatum (Doll.) Ching (AM)	Aerial Part	[22]
2.	Dryopteris austriaca (Jacq.) Woyn. ex Schinz & Thell.	Rhizome	[28]
3.	Dryopteris borreri (Newm.) Newm. ex Oberh. & Tave	Arial Part	[29]
4.	Dryopteris cambrensis (Fras.-Jenk.) Beitel & W.R. Buck	Arial Part	[29]
5.	Dryopteris caucasica (A. Braun) Fraser-Jenk. & M.F.V. Corley	Rhizome	[47]
6.	Dryopteris cochleata (D. Don) C. Chr.	Rhizome	[25]
7.	Dryopteris dilatata (Hoffm.) A. Gray	Rhizome	[30]
8.	Dryopteris fragrans (L.) Schott	Whole plant	[26]
9.	Dryopteris oreades Fomin	Arial Part	[29]
10.	Leucosidea sericea Eckl. & Zeyh.	Leaves and flowers	[21]
11.	Mallotus oppositifolius (Geiseler) Müll.Arg.	Leaves	[27]
12.	Syzygium polyanthum (Wight) Walp.	Leaves	[23, 24]

II. PHARMACOLOGICAL ACTIVITY

1. **Anti-Microbial Activity:** Antimicrobial agent kills or stops the growth of microorganisms. These agents can be grouped according to the primary action against the microorganisms e.g. antibiotics are used against bacteria and antifungals are used against fungi [31]. The World Health Organization's ((WHO) 1996 report underlines the severity of the global emergency in infectious diseases, with nearly 50,000 people dying every day from preventable or treatable illnesses, some costing as little as 1 dollar per person. Over the last two decades, around 30 new diseases have emerged, threatening the health of millions. Major diseases such as infectious diseases malaria, cholera, and tuberculosis are resurging, while new highly infectious diseases like HIV/AIDS and Ebola pose additional threats. The resistance against antibiotics is a growing concern, endangering the efficiency of life-saving drugs. As per the health figure infectious diseases are now the leading cause of premature death worldwide, claiming over 17,000,000 lives in 1995, including 9,000,000 young children. This report emphasizes the need for global solidarity and increased investment in disease control to protect communities and foster development [32]. Aspidinol isolated from the petroleum ether extract of the flowers and leaves of *Leucosidea sericea* Eckl. & Zeyh. evaluated for anti-microbial activity against the bacteria (*Bacillus subtilis, Staphylococcus aureus, Shigella sonnei, Escherichia coli, Salmonella typhimurium, Klebsiella pneumonia and Pseudomonas aeruginosa*) and yeast (*Candida albicans*). The results indicated that the plant has antimicrobial activity against *Staphylococcus aureus, Candida albicans* and *Bacillus subtilis* by using disk diffusion method [21]. The anti-dermatophyte activity of Aspidinol was evaluated against the microorganism named *Trichophyton rubrum, Trichophyton mentagrophytes, Gypsum*

microspore, and *Microsporum canis*, by using microdilution method. The minimal inhibitory concentrations (MICs) and minimal fungicidal concentrations (MFCs) against the four dermatophytes were determined. The anti-dermatophyte mechanism of compounds on cytochrome P450 sterol 14a-demethylase, β-1,3-glucan synthase and squalene epoxidase was investigated by the enzyme-linked immune-sorbent assay. It has the strongest anti-dermatophyte activity, especially against *M. canis* with the MIC value of 10 μg/mL. Terbinafine hydrochloride and Miconazole nitrate were used as standard drugs [33]. Aspidinol isolated from the leaf of *Dryopteris fragrans* tested for anti-bacterial activity against clinically isolated methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA) ATCC 29213 and ATCC 33591 using *in vitro* and *in vivo* methods. Aspidinol showed considerable anti-MRSA activity, both *in vitro* and *in vivo* (minimum inhibitory concentration- 2μg/mL) and model. It showed potent action against both MSSA and MRSA, with MICs and MBCs ranging from 0.25 to 2μg/mL and 0.5 to 4μg/mL, respectively. The killing kinetics of aspidinol was further assessed. The action of Aspidinol was comparable to vancomycin. Aspidinol or vancomycin at the dose of 50 mg/kg provided considerable protection from mortality, in the lethal septicemic mouse study. Aspidinol and vancomycin showed a major decrease in mean bacterial load in murine organs, including the liver, lung, and spleen in a non-lethal septicemic mouse study. The RNA-seq and RT-PCR analysis demonstrated that the inhibition of the development of ribosomes was the primary *S. Aureus* cell-killing mechanism of the tested compound, inhibition of the synthesis of amino acid and the decrease of virulence factors might has a secondary role [34].

2. **Anti-Malarial Activity:** Malaria, a devastating mosquito-borne disease, presents several key facts that underscore its global impact. According to the WHO, approximately 50% of the global population, primarily in sub-Saharan Africa (south of the Sahara Desert), remains at risk of contracting malaria. In 2019, an estimated 229 million cases of malaria occurred worldwide, leading to nearly 409,000 deaths, with the majority being young children in Africa. Pregnant women are also vulnerable, as malaria infection can lead to adverse outcomes such as stillbirths and low birth weight. The ailment is triggered by Plasmodium parasites, transmitted through the bites of infected female Anopheles mosquitoes. Although progress has been made in reducing malaria-related mortality through interventions like insecticide-treated bed nets and effective antimalarial treatments, continued efforts are crucial to combat this global health threat and strive toward its elimination [35]. Early reports have identified certain phytoconstituents as effective anti-malarial compounds, showcasing their potential in malaria treatment. These natural plant-derived substances have shown promise as alternative remedies to combat the disease [36]. The discovery of the 1st anti-malarial compound, quinine, was initiated later than its isolation in 1820 from the bark of *Cinchona* species (*Rubiaceae*). Chloroquine (CQ), synthesized in 1940, was also found to be effective against malaria. However, due to comprehensive and prolonged use, the parasites, especially *P. falciparum*, developed drug resistance against the chloroquine. The emergence and swift propagation of multidrug-resistant (MDR) strains of *P. falciparum* became a significant constraining element for the prevention and management of malaria. Presently, combination therapy (CT), including artemisinin and its derivatives, is suggested by the World Health Organization (WHO) as the most effective treatment for resistant strains. Aspidinol was evaluated for anti-malarial activity against the W2 strain and D6 strain of *Plasmodium falciparum*. It showed considerable action against *P. falciparum* [37].

3. **Anti-Parasite/Anti-Protozoal Activities:** Parasitic diseases (PD) are caused by organisms that live on or inside another living organism (host) and rely on the host for nourishment and survival. PD impacts both humans and animals, and is commonly spread through various pathways, including tainted water and food, insect stings, or direct interaction with infected individuals or animals. [38]. Earlier reports showed the potential of phytoconstituents as a bioactive substance to target various types of parasites, including protozoa, helminths, and other infectious organisms. Some well-known examples of anti-parasitic phytoconstituents include artemisinin from *Artemisia annua*, which is effective against malaria [39], and berberine found in various plants, which has shown activity against protozoan parasites like *Entamoeba histolytica*. The use of phytoconstituents as anti-parasitic agents presents a promising possibility for developing alternative treatments and combating parasitic infections [40]. Leishmaniasis is a ailment caused by protozoan parasites spread through female sandflies, with various clinical manifestations such as visceral and cutaneous leishmaniasis. As per the reports available, an approximate 350 million people are at risk of infection globally, with an yearly incidence of 1.5-2 million cases and around 70,000 deaths. Leishmaniasis is considered one of the neglected tropical diseases, and its prevalence is closely linked to poverty [41]. Aspidinol, isolated from the *Mallotus oppositifolius* leaves was evaluated for trypanocidal activity (*in vitro*) against the *Trypanosoma brucei brucei* trypomastigotes (CMP fast strain). It presented weak activity (LC100 = 100 μM). The pentamidine and Melarsoprol were used as reference drugs (LC100 value was 0.4 μM and 0.006 μM, respectively) [22]. Aspidinol B, the leaves of *Mallotus oppositifolius* was tested against *Leishmania donovani* promastigotes. It displayed weak anti-leishmanial activity against *L. donovani* promastigotes, with an EC50 value of 38.8 μM while the EC50 value of pentamidine (reference drug) was 7.7 μM [22]. Aspidinol, isolated from essential oil of the fern *Dryopteris dilatata* was found weak active in the *in-vitro* study against *Hymenolepis nana* at pH 8-5 and 37° C in 24 Hours at 1:100,000 (Minimum lethal Substance concentration). In *an in- vivo* study, up to 100mg/kg, it was found inactive against the dwarf tapeworm *Hymenolepis nana* [30].

4. **Cytotoxic Activity:** Phytoconstituents with cytotoxic activity can target and disrupt the structure or function of cancer cells, leading to their death through various mechanisms, such as inducing apoptosis (programmed cell death) or inhibiting cell division. It is an important property in the development of anti-cancer drugs, as these substances aim to specifically target and eliminate cancer cells while minimizing damage to healthy cells. Pharmaceutical researchers often screen various compounds for their cytotoxic activity to identify potential drugs for the treatment of cancer, liver and heart diseases [42]. Aspidinol isolated from the leaf of *Dryopteris fragrans* was tested for Cytotoxic activity toward macrophage cells (RAW264.7) by using MTT assay and ELISA method. The cells were exposed to aspidinol for a duration of 24 hours at varying concentrations spanning from 0 to 128 μg/mL. Assessments of cytotoxicity revealed that Aspidinol exhibited minimal harm to macrophage cells (RAW264.7). Even at the highest dosage tested, 128 μg/mL, aspidinol demonstrated no adverse effects on RAW264.7 cells. [43]. Aspidinol isolated from ethanol extract of *Dryopteris fragrans* (L.) Schott whole plant was evaluated for Cytotoxic activity against A549 (human lung cancer), MCF7 (human breast cancer) and HepG2 (human liver cancer) cancer cell lines by the MTT assay. It exhibited a significant cytotoxic action against MCF7 and A549 cell lines (IC50 10.58 ±1.56 μM and 12.59 ±2.74 μM). Pseudolaric acid B was used as a standard drug (IC50 =2.44 ±0.33 μM and 2.81 ±0.45 μM) [22]. 3T3-L1 (murine preadipocyte cell line) is a fibroblast-

derived cell line obtained from the mouse embryo. It is employed to investigate fundamental cellular pathways and mechanisms linked to diabetes, obesity, and related ailments. [44]. Aspidinol, isolated from ethanol extract of *Potentilla longifolia* aerial parts was evaluated for cell toxicity against lipid accumulation in 3T3-L1 Cells using MTT assay at various concentrations (0–80 μM). *Potentilla longifolia* Wild. ex D.F.K.Schltdl. (Whole plant) is generally used to treat liver injury diseases and jaundice in Chaoyao medicine (China). In this study, no toxicity was observed from 0–20 μM concentrations. The suppressive effect of Aspidinol at non-toxic concentrations on lipid buildup in 3T3-L1 cells was evaluated through visual and quantitative analyses of lipid content using Oil Red O staining, along with measurement of triglyceride levels. The outcomes from Oil Red O staining demonstrated that in comparison to the group treated with differentiation medium (DM), there was a reduction in the accumulation of lipid droplets in the 3T3-L1 cells treated with Aspidinol D (used as a reference compound in the positive control). This reduction indicated a partial inhibition of the differentiation of 3T3-L1 cells. At 0–20 μM concentration it showed no toxicity. It concluded that Aspidinol considerably curtailed the differentiation process and lipid accumulation in 3T3-L1 cells. This study proposes that Aspidinol will have a notable role in the future management of disorders connected to lipid accumulation. [45].

5. **Anti-Cancer Activity:** Worldwide, cancer is a significant global health concern and a leading reason for mortality. According to WHO, an estimated 9.6 million people died from cancer in 2018. The disease manifests in various forms, with lung, breast, colorectal, and prostate cancers being the most commonly diagnosed types. Additionally, nearly one in six deaths globally can be attributed to cancer, making it a major public health challenge. Early detection and timely treatment are crucial for improving cancer outcomes, and raising awareness about risk factors and prevention measures is essential in the fight against this devastating disease [46]. Aspidinol showed *in vitro* anti-tumor promoting effect on Epstein Barr virus early antigen (EBV-EA) activation induced by the tumor promoter 1 Z-O-tetradecanoylphorbol- 13-acetate (TPA) [48].

III. CONCLUSION

The pharmacological potential of Aspidinol has been a subject of growing interest. Aspidinol has demonstrated several promising medicinal properties, including anti-microbial, anti-parasitic, anti-malarial, and anti-cancer activities. These findings spark the interest in exploring its potential applications in healthcare and drug development. However, further researches are necessary to fully understand the mechanisms of action Aspidinol and to uncover its full therapeutic potential. In light of the global challenges posed by infectious diseases, parasites, and cancer, the potential applications of Aspidinol in healthcare offer a promising avenue for addressing these pressing issues.

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