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**INDO AMERICAN JOURNAL OF  
PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.344927>Available online at: <http://www.iajps.com>**Review Article****THERAPEUTIC AND BIOLOGICAL ACTIVITIES OF  
DAPHNE MUCRONATA- A REVIEW**

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**Received:** 01 February 2017**Accepted:** 08 February 2017**Published:** 28 February 2017**Abstract:**

*Phytochemical analysis showed that Daphne mucronata contained coumarins, flavonoids, triterpenoids, diterpene, sterols, lignin cumarinolignans, glucosides, daphnecin, aquillochin, daphnine and umbelliferone. Pharmacological studies revealed that the plant possessed antimicrobial, cytotoxic, analgesic, antiinflammatory and antioxidant effects. This study was designed to highlight the chemical constituents, pharmacological and therapeutic effects of Daphne mucronata.*

**Keywords:** *Daphne mucronata, pharmacology, therapeutic, constituents*

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**INTRODUCTION:**

In recent years, ethno medicinal studies has received much attention as this brings to light the numerous little known and unknown medicinal virtues especially of plant origin which needs evaluation on modern scientific lines such as chemical analysis, pharmacological, therapeutic, toxicological studies and clinical trials [1-25]. Phytochemical analysis showed that *Daphne mucronata* contained coumarins, flavonoids, triterpenoids, diterpene, sterols, lignin cumarinolignans, glucosides, daphnecin, aquillochin, daphnine and umbelliferone. Pharmacological studies revealed that the plant possessed antimicrobial, cytotoxic, analgesic, antiinflammatory and antioxidant effects. This study was designed to highlight the chemical constituents, pharmacological and therapeutic effects of *Daphne mucronata*.

**Synonyms:**

*Daphne angustifolia* K. Koch, *Daphne angustifolia* var. *mucronata* (Royle) Keissl, *Daphne angustifolia* var. *affghanica* (Meisn.) Pobed, *Daphne acuminata* Stocks, *Daphne acuminata* Boiss. & Hohen, *Daphne acuminata* var. *kochii* Meisn, *Daphne argentea* E. D. Clarke, *Daphne cachemireana* Meisn, *Daphne coriacea* Royle, *Daphne escalerae* Pau, *Daphne mucronata* var. *affghanica* Meisn [26-28].

**Taxonomic classification:**

**Kingdom:** plantae; **Phylum:** Tracheophyta; **Class:** Equisetopsida; **Subclass:** Magnoliidae; **Superorder:** Rosanae; **Order:** Malvales; **Family:** Thymelaeaceae; **Genus:** *Daphne*; **Species:** *Daphne mucronata* [29].

**Common names:**

**Arabic:** Daphne kabir el-azhar; **English:** Daphne; **Persian:** Kheshek, Khesht-e-garmsiri [30-31].

**Distribution:**

The plant was distributed in Turkey, Iran, Iraq, Oman, Saudi Arabia, Afghanistan and Pakistan [32].

**Description:**

Shrubs up to 2.5 m tall. Younger branches often tomentose. Leaves alternate or scattered, 3-5.8 cm long, 0.4-1 cm broad, elliptic-oblong to lanceolate, mucronate, less often obtuse, coriaceous, sessile. Flowers white, in axillary or terminal clusters, subsessile. Corolla tube 6-8 mm long, tomentose, dilated at the base, 4-lobed; lobes ovate to obovate, c. 4 mm long, spreading. Stamens 8, 2-seriate, upper 4 antisealous, subsessile. Ovary ovoid, c. 2.5 mm

long, pubescent. Style absent; stigma capitate. Berry subglobose, c. 10 mm long, pubescent, orange [27].

**Traditional uses:**

The plant was well known for its ethnopharmacological importance and was employed in traditional medicine for the treatment of various diseases including cleaning eyes and for eye pain. Its liniment was used for treating infectious wounds. It also used for muscular pain relieving, weary muscles by direct exposure to the smoke of branches or steam of its water extract. Its decoction and cooked leaves were employed for curing women infertility, gynecological infections, menstruation disorders and constipation [31, 33].

**Chemical constituents:**

Phytochemical analysis showed that the plant contained coumarins, flavonoids, triterpenoids, lignin cumarinolignans, glucosides, daphnecin, aquillochin, daphnine and umbelliferone [31]. Daphnecin, a coumarinolignan, aquillochin, umbelliferone and coumarin were isolated from the ethyl acetate-soluble fraction of *Daphne mucronata* [34]. However many chemical groups were isolated from *Daphne mucronata*. These included **Coumarins:** 7,8-Dimethoxycoumarin; **Carboxylic acids:** Cinnamic acid; **Flavonoids:** 5,7,3',4'- Tetrahydroxyflavone, 5,3',4'- Trihydroxyflavone 7- O-β-D-Glucopyranoside; 5,6,7,8,3',4'- Hexamethoxyflavone; 5-Hydroxy-3,6,7,4'- Tetrahydroxyflavone; **Triterpenoids:** Lupeol; Betulin; β-Amyrin; **Sterols:** Stigmasterol 3-O-β-D-Glucopyranoside; **Coumarinolignan:** Daphnecin and **Diterpene:** Gnidilatimonoein [31, 34-36].

**Pharmacological effects:****Cytotoxic effects:**

*Cytotoxic activity of the ethanolic extract of different parts of Daphne mucronata was studied using Artemia salina (brine shrimp). LD<sub>50</sub> values were determined in mg/ml. Alcoholic extract of leaves was the most effective extract (LD<sub>50</sub>=403 mg/ml) [37].*

The cytotoxicity of *Daphne mucronata* extract and one of its active purified components was evaluated using seven different cancerous cell lines. The extract possessed strong antiproliferative activity, with the using of flow cytometry technique, it was found that the most responsive cells are (K562), the progression of cells was inhibited at G1 phase by 15% compared to the untreated cells. Based on the extent of [<sup>3</sup>H]- thymidine and [<sup>3</sup>H]-uridine incorporation into DNA and RNA, respectively, the major effects of *Daphne mucronata* were on DNA and to a less extent on RNA synthesis [38].

The cytotoxic activities of two hydroalcoholic and chloroformic extracts of *Daphne mucronata* were examined on seven different cell lines [SK-Br-3 and MDA-MB-435 (breast cancer), Hela (cervical epitheloid carcinoma), K562 (myelogenous leukemia), U937 (monoblastic leukemia), Ag.8 (mouse myeloma) and Vero (primary monkey kidney)] by MTT assay. The highest cytotoxic activity of the hydroalcoholic extract of *Daphne mucronata* was exerted on breast cancer cell lines. 50 mg/ml of the extract inhibited proliferation of 24-hour cultures of MDA-MB-435 and SK-Br-3 cell lines by 73% and 34%, respectively). The extract showed anti-leukemic activity particularly against the U937 cell line. A 50% inhibition of cell proliferation (in 100 mg/ml of the extract) in 24-hour culture of U937 and 48-hour culture of Ag.8 cell lines was observed. The result of MTT assay showed a reduction of Hela cell line viability after 24-hour exposure to 10-50 mg/ml of the extract, but a significant stimulatory activity at concentrations more than 400 mg/ml was noted. No significant cytotoxic effect was detected in relation to the Vero cell line. The chloroformic extract showed weak cytotoxic effect on MDA-MB-435, SK-Br-3 and U937 cells but had no significant effect on the other cell lines [39].

The effect of *Daphne mucronata* purified diterpene was investigated on culture of human monocytes and two human leukemia cell lines (K562, CCRF-CEM). Fifty percent of growth inhibition was shown by 160  $\mu$ l (1:100 dilution, 0.5 g of the powdered leaves/ml) of the extract and 0.94 nM of the purified component, and there was more inhibition in K562 cells ( $P < 0.05$ ). Four fold increases in growth inhibition was shown in culture of isolated human monocytes and leukemia cell lines. There was a direct relationship between monocytes TNF- $\alpha$  secretion and growth inhibition degree. The authors concluded that *Daphne mucronata* extract and its purified diterpene potentially inhibit Leukemia cell line through increasing monocytes TNF- $\alpha$  releasing [40].

Promyeloblastic (KG1), promyelocytic (NB4) and promonocytic (U937) cells were cultured in the presence of various concentrations of the gnidilatimonoein (0.5-3.0 microM) for 3 days. It induced differentiation and apoptosis in KG1, NB4 and U937 cells. It inhibited growth and proliferation of KG1, NB4 and U937 cells with IC<sub>50</sub> values of 1.5, 1.5 and 1.0 microM, respectively, after 72 h of treatment. Cell viability was also decreased by 18%, 20% and 23%, respectively, after 72 h. Gnidilatimonoein at 0.5-1.5 microM induced differentiation by 5-50% in the cells, acridine

orange/ethidium bromide (AO/EtBr) double staining and DNA fragmentation assays revealed that apoptosis occurred after differentiation of the cells [36].

IMPDH (inosine 5'-monophosphate dehydrogenase) is the rate-limiting enzyme in the de novo biosynthetic pathway of guanine nucleotides, which was up-regulated in human leukaemia cell lines. Gnidilatimonoein, isolated from *Daphne mucronata*, was IMPDH inhibitor and a strong antiproliferative agent. The effects of gnidilatimonoein on intracellular GTP pool size and its link to differentiation and apoptosis of K562 cells were evaluated. Gnidilatimonoein inhibited cell proliferation and induced G0/G1 cell cycle arrest in K562 cells after 24 h exposure to a single dose of gnidilatimonoein (1.5  $\mu$ M), while no significant effects were observed on unstimulated and phytohaemagglutinin-stimulated peripheral blood lymphocyte cells at the gnidilatimonoein dose (1.5  $\mu$ M). Based on the morphological changes, Wright-Giemsa staining, benzidine assay and the expression of cell surface markers [GPIIb (glycoprotein IIb) and glycophorin A], K562 cells had differentiated towards megakaryocytic lineage. In addition, gnidilatimonoein induced apoptosis among K562 cells based on acridine orange/ethidium bromide and annexin V/propidium iodide double-staining observations. These changes, which were abrogated by the addition of guanosine, became evident when the intracellular GTP level decreased to approximately 20-35% of the untreated control level. The authors concluded that gnidilatimonoein induced differentiation and apoptosis in K562 cells through perturbation of GTP metabolism, as one of its mechanisms of action [41].

Gnidilatimonoein, a diterpene ester isolated from from *Daphne mucronata*, possesses strong anti-metastasis and anti-tumor activities. The apoptosis and differentiation capabilities of gnidilatimonoein were evaluated by using the leukemia HL-60 cell line. It decreased the growth of the cells dose- and time-dependently and the IC<sub>50</sub> was found to be 1.3  $\mu$ M. The results revealed that gnidilatimonoein induced both monocytic differentiation and apoptosis among HL-60 cells. In addition, cell cycle analyses showed an increase in G1 phase population by 24 hrs, which was gradually replaced by Sub-G1 cell population (apoptotic cells) by 72 hrs. The authors concluded that gnidilatimonoein might be a good candidate for differentiation therapy of leukemia [42].

Alteration of the cell surface glycoproteins of cancerous cells correlate with malignancy potential.

The mediation of membrane glycoproteins in wehi-164 cancerous cells, under the effect of *Daphne mucronata* crude extract and one of its purified active components, and their attachment to fibronectin-coated wells were investigated. The plant extract, 27 microl/ml (equivalent to 0.54 mg/of plant leaves powder per ml of culture medium), as well as gnidilatimonoecin (0.94 microM), were capable of quenching (by 58% and 64%, respectively), the attachment of wehi-164 cells to fibronectin-coated wells (4 microg/ml). In addition to alteration of cell adhesive properties, the morphology of the treated cells were significantly changed upon treatment with the non-toxic dose of the plant extract or gnidilatimonoecin. Furthermore, the untreated cells have polygonal shapes, while, the treated cells appeared with spherical shapes [43].

The adhesion of thrombin activated human platelets to the cultured monocytes or HL-60 cells was investigated under the effect of *Daphne mucronata* extract [(0.54 mg/ml) or one of its purified components (gnidilatimonoecin, 0.94  $\mu$ M)], as the adhesive interaction between tumor cells and the host cells or the extracellular matrix played a crucial role in tumor metastasis. Treatment of the platelets with the plant extract or the active component, for various time intervals, followed by their activation by thrombin resulted in 80-90% reduction in the number of monocytes with more than 10 attached platelets. Similarly, under almost all identical conditions, the adhesion of the activated platelets to HL-60 cells was decreased by 90%. The adhesion of thrombin activated human platelets to the plant treated HL-60 cells was also reduced significantly (by 95%) [44].

Cytotoxicity evaluation of gnidilatimonoecin revealed the strong antiproliferative activity among several different human cancer cell lines (K562, CCRF-CEM, HL-60 and MOLT-4 leukemia cell lines, LNCaP-FGC-10 a prostate cancer cell line) and a mouse BALB/C fibrosarcoma cell line (WEHI-164). The treatment with gnidilatimonoecin inhibited the progression of (K562) cells in G1 phase by almost 15% compared to the untreated cells. The population of the treated cells in the S and G2 phases also reduced by 8.3% and 5.4%, respectively. Based on the extent of [3H]-thymidine and [3H]-uridine incorporation into DNA and RNA, respectively, the major effects of gnidilatimonoecin were found to be mainly on DNA and to a less extent on RNA synthesis. Additionally, the activity of inosine-5'-monophosphate dehydrogenase (IMPDH), was reduced under the effects of genidilatimonoecin by 44% [45].

Oral administration of an alcohol extract of *Daphne mucronata* to a group of breast tumor bearing rats, for more than 20 consecutive days, reduced significantly the diameter of tumor and eliminated them totally if the treatment continued for a longer time. To study the mode of antineoplastic of the plant, the effects of the plant extract were evaluated on the human tumor necrosis factor alpha (hTNF-  $\alpha$ ) release and TNF-  $\alpha$  receptor regulation in the cultured human monocytes in the presence or absence of bacterial lipopolysaccharide (LPS). The results revealed that the plant extract at various doses, slightly increase TNF-  $\alpha$  secretion by the cultured monocytes. In addition, the plant extract down-regulated the TNF-  $\alpha$  receptors in a time dependent manner [46].

#### **Antimicrobial effects:**

Antibacterial and antifungal activity of the ethanolic extract of leave and stem of *Daphne mucronata* were evaluated against four species of Gram positive and Gram negative bacteria and two fungi. The results showed that extracts were active against *Escherichia coli* and *Staphylococcus aureus*, however, ethanolic extract of the roots of plant were the most effective against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*). The leaves and stems extract of the plant had no effect on *Pseudomonas aeruginosa* even at high concentration. Antifungal activity was not observed in any part of the plant [37].

Biofilms protect the pathogens from inhibitory effect of antibiotics and immune cells. *Pseudomonas aeruginosa* was an important pathogen, and one of the hallmarks of *Pseudomonas aeruginosa* infection was its capability to adhere to, and propagate on medical devices, such as catheters, contact lenses, and wound dressings by forming strong biofilms. Antipseudomonal activity of *Daphne mucronata* 5% aqueous extracts was determined using Disk-Diffusion assay. *Daphne mucronata*, produced zone of inhibition of 12mm, biofilm reduction 40.08% and biofilm removal 46.02% [47].

#### **Analgesic and anti-inflammatory effects:**

The analgesic and anti-inflammatory effects of ethyl acetate extract of aerial parts of *Daphne mucronata* and the possible involvement of opioid receptors were studied in mice using formalin test. Single doses of 2.5, 5.0 and 10.0 mg/kg bw of ethyl acetate extract of *Daphne mucronata* were intraperitoneally administered to the mice 30 min before carrying out the analgesic test. The results revealed that the extract (2.5, 5.0 and 10.0 mg/kg) increased the pain threshold of mice and induced analgesia in both

phases of formalin test. Like morphine sulfate (5.0 mg/kg, ip), the extract also showed more effective analgesic effect on the late phase of formalin test. Pre-treatment of animals with naloxone (5.0 mg/kg ip) did not inhibit the effects of the extract [48].

#### Antioxidant effect:

The antioxidant activity of eleven compounds isolated from *Daphne mucronata* was studied using DPPH assay. Compound 5,7,3',4'-tetrahydroxyflavone and 5,3',4'-trihydroxyflavone 7-O-β-D-glucopyranoside showed moderate antioxidant activity while, other compounds including (cinnamic acid, 7,8-dimethoxycoumarin, 7,8-dihydroxycoumarin, lupeol, Bamyryn, betulin, 5,6,7,8,3',4'-hexamethoxyflavone, 5-hydroxy-3,6,7,4'tetramethoxyflavone, and stigmaterol 3-O-β-D-glucopyranoside) were weak antioxidants [35].

#### CONCLUSION:

The current review highlights the chemical constituents, pharmacological importance of *Daphne mucronata* as promising herbal drug because of its safety and effectiveness.

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