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Review on Role of Herbs as Anticancer

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Abstract:

This Report has been made to review some medicinal plants used for the treating cancer disease. The plant sources of India are likely to provide effective anticancer agents. Herbs have a vital role in the prevention and treatment of cancer. Examples are provided in this review of promising bioactive compounds obtained from various plants with medicinal and other therapeutic uses. The photochemical exploration of these herbs has contributed to some extent in this race for the discovery of new anticancer drugs. In recent years owing to the fear of side effects people prefer to use of natural plant products for cancer treatment. This review also helps to summarize the diverse methodologies and various ways to evaluate the potential natural compounds having anticancer activity.

Although drug discovery from medicinal plants continues to provide an important source of new drug leads, numerous challenges are encountered including the procurement of plant materials and their selection

INTRODUCTION

Herbs have used in the traditional system of medicine since time immemorial to alleviate human illness and for the maintenance of general health.

As per WHO, 80% of world population of the developing countries still rely on the crude drugs and folklore medicines for their primary health care needs.

The interest of people in herbal medicines has increased significantly in both developed and developing countries.

There is a great demand for herbs, hence there is a need to adopt systematic scientific methods for their selection, cultivation, collection, processing and to ensure the quality, purity, safety, potency and develop modern methods for their quality control so that maximum benefit is obtained from these herbal medicines

contamination & serious health hazards to doctors, nurses, ward boys, support staff, sanitation workers, rag pickers & other health care workers. Who are regularly exposed to biomedical waste as an occupation hazards as well as general public in the surrounding area .

Spices

Spices are fruits, roots, barks, seeds, or any other plant substance used primarily in flavoring, or for the coloring and preservation of food.

Spices often have antimicrobial properties, and they are occasionally ground into powder for convenient usage. Spices are more commonly used in climates that are warm, since these climates are far likelier to have outbreaks of infectious diseases, as compared to climates that are comparatively colder or cooler. Spices are mostly used in religious rituals, medicines, perfumes and cosmetics, or as vegetables

Nutritional Value of Spices

Spices generally have strong flavours, and due to the fact that they are used in small quantities, they don't add a lot of extra calories to the food. Some spices contain considerable portions of protein, fats, and carbohydrates. Spices like paprika contains a large amount of Vitamin A. If used in larger quantities, spices contain substantial amounts of iron, minerals, magnesium and calcium.

Most spices are said to have antioxidant properties, and they also possess phenolic compounds such as flavonoids, which help in the absorption of nutrients

Role of Herbes on Cancer

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.
Not all tumors are cancerous: benign fumors do not spread to other parts of the body. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. While these symptoms may indicate cancer, they may have other causes. Over 100 types of cancers affect humans.
These diseases are characterized by a cellular malfunction. Healthy cells are programmed to know what to do and when to do it. Cancerous cells do not have this programming and therefore replicate and grow out of control.Cancerous cells in together are called Neoplasm

Different herbs role on cancer
Potential Health Effects of Various Culinary Herbs Indicated in Scientific Literature

Herb	Bioactive compound / Tested Sample	Percevied Health
Basil (ocimum basilicum)	Eugenol and flavonoids	anti-inflammation in cancer develop , Anti-microbial effects
Ginseng	Herb extract	hypoglycemic effect
Lemongrass	Citral,limonene	Anti-inflammation and inhibition of Polymine biosynthesis in human Colon cancer development
Oregano	Herb extract	Antimicrobial effect
Parsley	Myristicin/herb extract	Inhibition of lung carcinogenesis Antimicrobial effect
Rosemary	Flavonoids	Inhibition of carcinogenesis
Sage	Essential oil	Inhibitation of bone resorption
Spearmint	Herb extract	Antimutagenic effect
Thyme	Thymol	Inhibition og bone resorption

Parmotrema perlatum (Dagadphool)

KALPASI (DAGAD PHOOL / BLACK STONE FLOWER)

Kalpasi, alternatively known as Dagad phool or black stone flower is a kind of lichen. This blackish purple mystery flower is often blended with other spices to make delectable masalas. It is a common spice used in Chettinad cuisine such as Chettinad masala and some
Maharashtrian dishes

Scientific Classification

- Domain: Eukaryota
- Kingdom: Fungi
- Division: Ascomycota
- Class: Lecanoromycetes
- Order: Lecanorales
- Family: Parmeliaceae
- Genus: Parmotrema
- Species: P.perlatum

Parmotrema perlatum

Some of the other names for it include shaileyam in Sanskrit, kalpasi in Tamil, dagar da phool in Punjabi, dagad phool in Marathi, raathi Pootha (banda puvvu) in Telugu, kallu hoovu in Kannada and patthar ke phool in Hindi, bojhwar and chadila inNorth.India.

What is the the taste of Dagad Phool?

By itself dagad phool is bitter. It tastes can be compared to being pungent & astringent. However, when added to a recipe and cooked it imparts a wonderful smoky flavour.
Dry ground kalpasi has little or no smell and should be roasted in little oil to get its actual and full aroma

What is the chemical composition of Dagad Phool? Know and understand about chemical Composition of Kalpasi or Stone Flower.

It contains many chemical constituents like

• tridecyl myristate, 3-ketooleanane, icosan-1-ol, usnic acid12,
• parmelanostene permelabdone14, atranorin, lecanoric acid,
• orcin, erythrolein, azolitmin and spaniolitmint

What are the Ayurvedic properties of Dagad Phool?

Know more about ayurvedic properties of Dagad Phool or Black Stone Flower.

• Rasa (Taste): Tikta (pungent), Kasaya (astringent)

• Guna (Property): Laghu (light), Snidha (slimy)

• Virya (Potency): Sheet (cold)

• Vipaka (Post digestive effect): Katu (bitter)

• Karma (Effect on dosha/disease): Hrdya (Heart diseases), Pittahara, Stambhaka (Semen thickening agent), Kapha-pitthara

- **Health Benefits of Dagad Phool as an Antidiabetic** – extract of P.

perlata showed significant antidiabetic activity compared to glibenclamide against alloxan induced diabetes in rats.

- **Health Benefits of Dagad Phool as an Antibacterial** - The methanolic, ethyl acetate and acetone extracts of P. perlata were found to have significant antibacterial activity against

Staphylococcus aureus.

- **Health Benefits of Dagad Phool as anAntiviral** - The antiviral properties were determined against yellow fever, poliomyelitis and infectious bursal disease virus.

Health benefits of Black Stone Floweragainst Asthma - Ayurvedarecommends Black

- Stone Flower as animportant herb for asthma management due to its Kapha-Vata balance

- **Health Benefits of Stone Flower as an Antiulcer** - There is evidence of Dagad Phool potential against cold restraint, aspirin, alcohol and pyloric ligation.

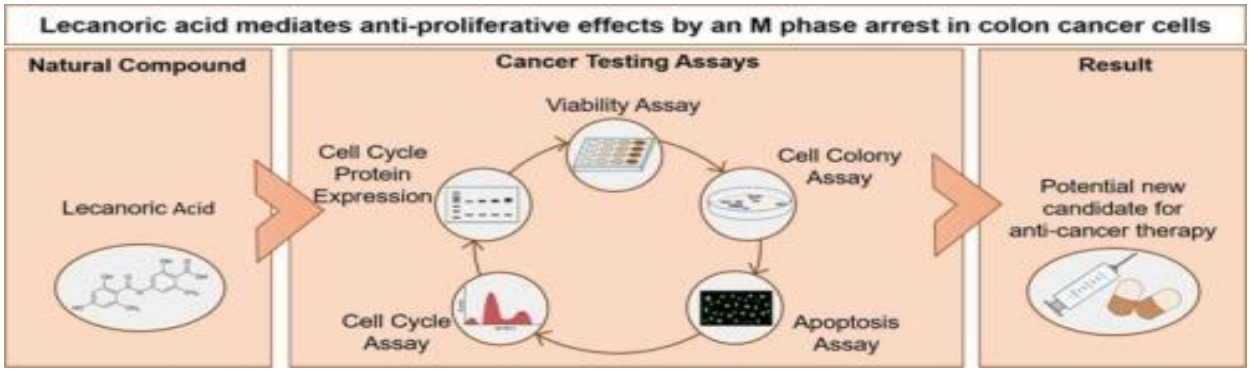
- **Health Benefits of Dagad Phool as an Antioxidant** - The ethanolic extract of dagad phool showed significantly good free radical scavenging effects and antioxidant potential.

- **Health Benefits of Kalpasi in Hypolipidemic** - Methonolic extract of P.perlata was proved to have significant hypolipidemic activity when tested by employing in-vitro anti-cholesterol assay.

- **Health Benefits of Kalpasi as Cytotoxic** agent - Methonolic extract of P. perlata was found to have cytotoxic activity and showed anti-proliferation against colon cancer cell

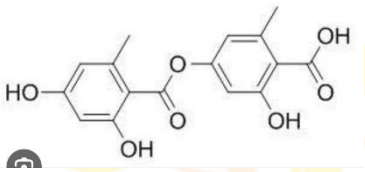
Role of parmotrema perlatum (Dagadphool) as anticancer:

Lecanoric Acid: Lecanoric acid and atranorin reduced viability in various cancer cell lines. Atranorin induced apoptosis in the cancer cell lines HCT-116 and HeLa. Lecanoric acid mediates its anti-proliferative effect via an arrest in the M phase. Lecanoric acid shows low toxicity in primary human immune and endothelial cells.



Chemistry of lecanoric acid

- **Structure:**



- **Molecular formula:** C16H14O7
- **Synoyms:** lecanoric acid 480-56-8 lecanorricacid o-orsellinate depside
- **Molecular weight:** 318.28 g/mol

Lecanoric acid is an orcinol depsidefound in a broad range of lichen and fungal species. Structurally, lecanoric acid is a dimer of orsellinic acid.Lecanoric acid is a broad antimicrobial agent, exhibiting more potent activity against bacteria than fungi. Lecanoric acid is also active as animmunomodulator,antioxidant, an inhibitor of histidine decarboxylase and is involved in geneactivation/suppression. Lecanoric acid isan important standard in thechemotaxonomy of lichens.

Performance of different assay

Materials and methods

Cells and reagents

HCT-116 and HEK293T were purchased from DSMZ GmbH (Braunschweig, Germany). RAW246.7, NIH3T3 and HeLa were obtained from ATCC (Virginia, USA). Primary human umbilical vein endothelial cells (HUVECs) were isolated from human umbilical cords according to Jaffe et al. HCT116 cells were cultivated in McCov's 5A (modified) medium, HEK293T in DMEM medium, NIHST3 cells in DMEM Gluta-MAX and HeLa as well as RAW264.7 cells in RPMI medium. These media contained 10% fetal calf serum (FCS) and 1% penicillin/streptomycin.

Primary HUVECs were cultured in EC growth medium (ECGM) (PELO.

Biotech, Martinsried, Germany) supplemented with 10% FCS (Biochrom AG), 100 U/ml penicillin, 100 g/ml streptomycin, and 2.5 g/ml amphotericin B (PAN-Biotech, Aidenbach, Germany), and a supplement mixture (PELOBiotech). HUVECs were used for experimental purposes exclusively in passage three. All cells were cultured at 37 °C in a 5% CO2 atmosphere. Atranorin was purchased from Biozol (Eching Germany).

Lecanoric acid and evernic acid were purchased from Ambinter c/o Greenpharma, (Orléans, France). Lichen metabolites were dissolved in DMSO and further diluted in media (maximal DMSO concentration during experiments 0.3%).

Cell colony assay

1000 HCT-116 cells were seeded per well in a 6-well plate and incubated for at least 5 h. Cells were treated with increasing concentrations atranorin (0.3, 3 ug/ml), evernic acid (0.3, 3 ug/ml), lecanoric acid (0.003, 0.03, 0.3 g/ml) or vehicle (DMSO) for 8 days. Cells were washed with PBS, fixed with a mixture of 6% glutaraldehyde and 0.5% cresyl violet acetate for 30 min. The glutaraldehyde/cresyl violet mixture was carefully removed and cells were rinsed with tap water.

Images were taken from each well and the area of the cell colonies per well was determined using the Image software. For this, images of the individual wells were cut out of the image of the 6-

Well plate, and the areas of the colonies determined with the multi-point tool. The colony area for
Vehicle samples was set to 100%, and the lichen metabolite treated samples were related to the vehicle sample

Apoptosis assay

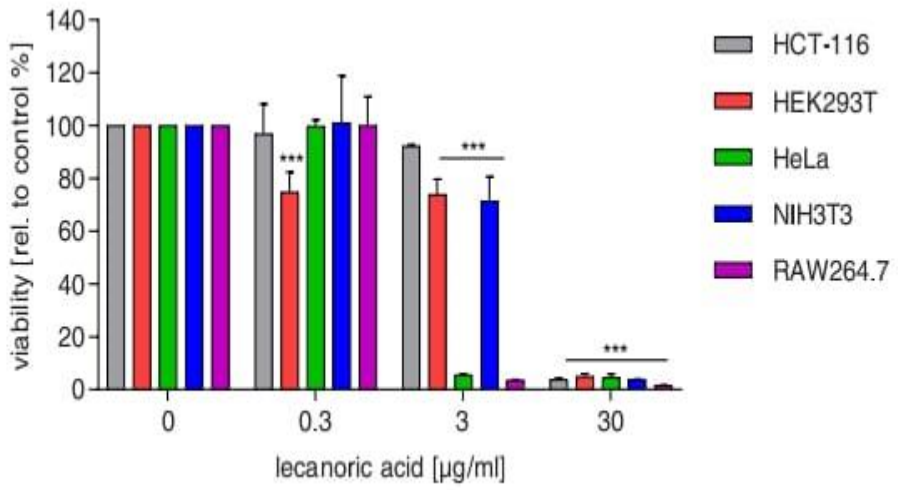
The apoptosis assay was performed on HCT-116 cells as previously described. Briefly, 2 × 105 HCT-116 cells were seeded in a black poly-D-lysin coated 96-well plate, cultured for 24 h, and subjected to the different lichen metabolites (0, 0.3, 3, 30 pg/ml) for 24 h. For apoptosis detection, cells were incubated with CellEvent Caspase 3/7 Green Detection Reagent (1:1000) (Thermo Fisher Scientific, Massachusetts, USA) for 90 min. Then, DRAQ5 (1:250) (BioLegend, California, USA) was added and incubated for an additional 30 min at room temperature.

Each well was examined with the ImageXpress Micro Confocal High Content Imaging System (Molecular Devices, California, USA). The number of apoptotic cells was determined using the MetaXpress 6
Software (Molecular Devices, California, USA).

Apoptosis of HUVECs was detected according to the method of Nicoletti et al. Cells were treated as indicated and were incubated overnight in the dark in a PBS solution containing propidium iodide (PI)
(50 g/ml; MilliporeSigma, Darmstadt, Germany), sodium citrate (0.1%;Carl Roth, Karlsruhe, Germany), and Triton X-100 (0.1%; Milli poreSigma) at 4 °C. The percentage of cells with sub-diploidic DNA content was measured using a FACSVerse flow cytometer (BD Bio-sciences, Heidelberg, Germany)

Cell cycle analysis

Cell cycle analysis was performed as previously described.Briefly, 2 × 105 HCT-116 were seeded in a 96-well cell culture plate and Cultured for 24 h. Cells were treated with the different lichen metabolites (0, 0.3, 3, and 30 g/ml) for 24 h. Afterwards, cells were harvested, suspended in 200 ul sample buffer (1 g/I glucose in PBS without Ca? + and Mg?+), mixed, centrifuged (200 g, 4 min, 4 °C) and the supernatant was discarded. This step was repeated once. The cells were fixed with 150 ul of ice-cold 70% ethanol overnight (> 18 h) at 4 °C. The cell pellet was washed with sample buffer, resuspended in 100 pl staining buffer (20 g/ml PI and 0.2 mg/ml RNase in sample buffer), and incubated for 40 min at room temperature. Samples were measured within 24 h in a MACSQuant Analyzer (Miltenyi Biotec GmbH, Bergisch Gladbach, Ger-many). Cell cycle distribution was determined using FlowJo V10.5.3 software



Result

Lecanoric acid increased the cell number in the G2 phase

Besides apoptosis, reduced cell viability can be mediated by cell cycle arrest. Therefore, we investigated whether the lichen metabolites influence cell distribution during different cell cycle phases. The cell cycle distribution of HCT-116 cells treated with increasing concentrations of the depsides for 24 h was determined by flow cytometry. For atranorin and evernic acid, no effects were observed on the cell cycle distribution in HCT-116 cells. Most interestingly, lecanoric acid at the low concentration of 0.3 g/ml significantly increased the cell number in the G2 phase, accompanied by a reduction of cells in the G1 and S phase. Cells in the subG1 phase, which represent cells undergoing late-stage apoptosis, also increased slightly. Since the influence of the secondary lichen metabolites on viability was cell type-dependent, we also investigated the effects of the depsides on the cell cycle distribution in other cell lines (HeLa, NIH3T3,RAW264.7). Already at 3 g/ mi, atranorin increased the number of HeLa cells in the subG1 phase confirming that atranorin induces apoptosis. Evernic acid had little impact on the cell cycle distribution in HeLa, NIH3T3, and RAW246.7

Cells. Lecanoric acid at 0.3 ug/ml increased the cell number in the G2 and subG1 phases in HeLa cells and at 3 pg/ml in NIH3T3 cells. In RAW246.7 cells, lecanoric acid increased cell number in the subG1 phase accompanied by a decrease of cells in the G1

and S phases. These data indicate that atranorin does not have a significant effect on the cell cycle distribution. Evernic acid may have little effect, and lecanoric acid arrests HCT-116, NIH3T3, and HeLa cells in the G2 phase

Lecanoric acid regulated expression levels of cell cycle proteins

Next, we evaluated whether lecanoric acid and evernic acid regulate cell cycle proteins in HCT-116 cells. We did not investigate the effect of atranorin on cell cycle proteins because no effect on the cell cycle distribution was observed with this compound. Several cell cycle proteins were investigated by western blotting, including cyclin E, which is required to overcome the G1/S checkpoint to commence DNA replica-tion, and p21, a cyclin-dependent kinase inhibitor that

Interacts with the cyclin E-CDK2-complex and thereby, stops the transition from Gl to S phase. Interestingly, lecanoric acid significantly reduced the expression of cyclin E but not of p21, whereas evernic acid had no effect.

For the transition of the S to the G2 phase, CDK1 and cyclin A are required. The kinases Mytl and Weel can inactivate CDK1 by phosphorylation at positions Tyr14 and Tyr15. The phosphatase pedc25C (active form) dephosphorylates pCDK1 at Tyr15 and thereb activates CDK1. Lecanoric acid reduced the expression of cyclin A, PCDK1 and pWeel (inactive form), whereas Mytl expression was not significantly influenced. Moreover, lecanoric acid significantly reduced the level of cde25C and increased pedc25C expression. Evernic acid only induced peel protein.

Traversing the G2/M checkpoint to initiate mitosis requires CDK1 as well as cyclin B and cyclin A. Phosphorylation of histone H3 (pH3) is correlated with chromosome condensation during mitosis.Moreover, we detected GADD454 as a marker for apoptosis.Lecanoric acid induced the expression of cyclin B1 and pH3, but did not affect GADD45A. With evernic acid, we observed no effect on cell cycle proteins involved in the G2/M transition. These data reveal that lecanoric acid arrests cells in the M phase rather than in the G2 phase.

Lecanoric acid did not influence the viability of primary peripheral immune and endothelial cells

Lecanoric acid did not influence the viability of primary peripheral immune and endothelial cells

A common side effect of anti-cancer drugs is to influence the viability of healthy cells, including immune cells. This is an unfortunate side effect, since functional cytotoxic innate and adaptive immune cells can aid in controlling cancer development.Therefore, we investigated whether lichen secondary metabolites also exert cytotoxic effects on peripheral blood mononuclear cells (PBMCs).

Treatment of PBMCs with lecanoric acid, evernic acid, and atranorin for 24 h did not significantly reduce cell viability. In addition we tested the effects of these compounds on the viability of primary human umbilical vein endothelial cells (HUVECs). After 24 h treatment with evernic acid and atranorin, the viability of HUVECs was not reduced (Supplementary. However, lecanoric acid at the highest concentration (30 g/ml), caused a 20% reduction in viability through effects on metabolic activity and an increase in apoptosis

Conclusion

Licanoric acid obtained from parmotrema parlatum as a promising candidate due to its mode of action as a cell cycle inhibitor and because of its low cytotoxic effects on primary immune and endothelial cells. In general, the idea to exploit cell cycle inhibitors as anti-cancer drugs is widely employed with the so-called CDK inhibitors. The first cell cycle kinase inhibitor, pal-bociclib which inhibits CDK4/6, is already approved for the treatment of breast cancer. Taken together, lecanoric acid represents an interesting compound that exerts valuable pharmacological actions in vitro in the context of cancer formation and development processes. As an additional plus, lecanoric acid can be biotechnologically synthesized

Our findings warrant further investigation of this promising natural product in a preclinical setting.

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