Potentilla fulgens: A Systematic Review on Traditional Uses, Pharmacology and Phytochemical Study with Reference to Anticancer Activity

Chandana Choudhury Barua*, Nilofar Yasmin

Department of Pharmacology and Toxicology, College of Veterinary Science, Assam Agricultural University, Guwahati – 781 022, Assam, India.

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Abstract

Potentilla fulgens has been extensively used in folk medicine by the local people of Meghalaya in North East India. Traditionally, the root-stock and the whole plant, Potentilla fulgens are utilized as astringent and tonic for curing the gums from tooth ailments. The aqueous root peel extract of this plant is consumed to get rid of intestinal infections and also the tap root is traditionally chewed along with betel nut (Areca catechu) and betel leaves (Piper betel) for various ailments. North East India has maximum incidence and occurrence of different types of oral cancer due to consumption of tobacco, tobacco related compounds and alcohol. Taking into consideration its high medicinal value and popularity of the plant, we have tried to compile and update the latest research work carried out by other workers and to explore its potential as anticancer therapy with a futuristic approach. Subsequently, the plant has been studied in detail on its various pharmacological activity by few researchers and two reviews were already published in the years 2009 and 2011, encompassing its pharmacological, taxonomical, phytochemical attributes. So, our aim was to explore the latest work done so far post 2011.

1. Introduction

Potentilla fulgens L (Family: Rosaceae) is a local medicinal plant, found in Northeast India, of the state Meghalaya. More than 6,500 species of medicinal plants are found in Northeast India. Scientific interest in the genus Potentilla and their curative properties originated from the realm of traditional medicine. They are known as cinquefoils in English, Bajradanti in Hindi [1], Ganeful and Dentamanjari in Nepali [2], Akanada and Dentamanjari in Uttarakhand, San geZil pa in Tibetan [1, 2] and lyniangbru (Khasi) in Meghalaya [2]. The roots of Potentilla fulgens are used for the treatment of colic pain, spasmodic trouble, pyorrhea and tumor [3]. Ethnographic groups of this region use leaves, bark, roots, shoot etc of Potentilla fulgens as a source of medicine [4]. The aqueous root peel extract of P. fulgens is consumed to get rid of intestinal parasitic infections. P. fulgens contains rich amount of polyphenols in stem, leaves and root, as a result, it is widely used for medicine in the Ayurvedic, Unani and Siddha systems of medicine in India [5, 6]. North-east India is one of the 25 global biodiversity hotspots which lies between 22-30° N latitude and 89-97° E longitude where the region is endowed with varied flora to its diversified topography and climatic conditions with high rainfall, moderate temperature and high humidity abound with dense forests, marshes, swamps etc., [3]. Different tribes living in this area mostly dependent on traditional herbal medicine for their primary health care services as herbal medicines are less toxic and have no side effects in comparison to the chemotherapeutic drugs also cheaper as preferring chemotherapeutic drugs is not always affordable for this people. So, the cheap herbal drug treatment may highly be recommended to the rural and poor people to treat effectively the cancers of various types is an ideal choice. More than 50% of all modern drugs in clinical use are of natural product origin, so keeping in mind the importance of herbal medicinal plants a thorough literature based search was primarily done to write this review on Potentilla fulgens as it is extensively found in North-east part of India.

In order to gather information the keywords “Potentilla fulgens or Potentilla or P. fulgens” and (traditional or therapeutic or medicinal or pharmacological uses)” and “cancer or anticancer or carcinogenic or anti-tumor activity and Potentilla fulgens or Potentilla or P. fulgens” were searched in databases such as Pubmed, ScienceDirect, Scopus, Google Scholar, a total of 55 articles were found, some nonrelevant articles were excluded and among them only two papers were found as review article [7, 8]. Potentilla fulgens and Potentilla species which were published in 2009 and 2011 respectively covered detail and elaborate information on pharmacological activity and phytochemical constituents. This review includes research work done post 2011 so that further studies and research work can be extended in new direction.

2. Scientific Classification of Potentilla fulgens

Kingdom : Plantae
Order : Rosales
Family : Rosaceae
Genus : Potentilla
Species : P. fulgens

3. Habitat

It grows in rocky terrains. They thrive in heavy soils. Propagation is done through seed, cuttings or division of rootstocks. It grows in regions with a temperate climate and at a height of elevation about 1800 – 4350 metres above sea level.

Fig. 1 Potentilla fulgens Wall. ex Hook. plant [a] and root [b]

4. Morphology

Typical cinquefoils looks most similar to strawberries. They have palmate leaves. They have fifteen or more leaflets arranged pinnately. The flowers are generally yellow in colour and flowering stems are 5-40 cm tall (Figs. 1 and 2). The accessory fruits are usually dry, but may be fleshy and strawberry-like, while the actual seeds – each one technically a single fruit – are tiny nuts. The plant have thick rootstock, erect perennial herb (15-75 cm) and thrives well in moist places.
5. Growth
Potentilla fulgens grows in open meadows and grassy slopes in the Himalayas. It gives leaves by May and flowers by June-July and starts to fruit by August and deteriorates by September. It reproduces from both the seeds and roots [9].

6. Taxonomy
Among the Rosaceae, cinquefoils are close relatives of avens (genus Geum) and roses (Rosa), and even closer relatives of agrimones (Agrimonia). Lady’s mantles (Alchemilla) and strawberries (Fragaria) are more closely related to Potentilla (Wikipedia).

7. Distribution
Potentilla fulgens which is commonly known as the Himalayan Cinquefoil and Lyngniangbru by the Khasi tribe of Meghalaya is widely found in North-east India as well as in Northern parts of India. It is found in the wild habitats of Meghalaya. Globally different species of Potentilla are found in Asia, Europe and North America, whereas species diversity is found highest in Northern Eurasia.

8. Utility and Edibility
The root stock as well as whole Potentilla fulgens are utilized for ethnological purposes. Fresh tap roots are pulverized, weighed and soaked in methanol to make the methanol extract which is used for biological activity [10]. The root is chewed with betel nut in North eastern part of India which is effective against high blood pressure, is safe to use as a homemade remedy [11]. Leaves, bark, root and shoots are the edible parts of Potentilla fulgens and commercially used by the local people for treatment of diseases.

9. Traditional and Medicinal Uses of P. fulgens
The aqueous root peel extract of this plant is consumed to get rid of intestinal parasitic infections. The root has anti-diarrheal properties and are effective against high blood pressure and is safe to use as a homemade remedy. Traditionally in Northeast India, the root-stock and the whole Potentilla fulgens is utilized as astringent and tonic for curing the gums from tooth ailments such as pyorrhea, toothache and caries and other tooth ache. Twigs and leaves of Potentilla fulgens are mostly used as toothbrush by the Bhutias in Uttarakhand in India. Leaf paste is used for curing stomach pain, cough, cold, throat soar and ulcer [10]. Roots are also used for treatment of wounds and tiger bites in Garhwal district of Himalayan region. Whole plant is used for stomatitis and aphthea. In countries like Nepal and Bhutan, plant juice is taken for treatment of peptic ulcer and dysuria [12].

Syiem et al., had done extensive work on Potentilla fulgens and reported that it can also prevent cell death and exhibit anti carcinogenic activity [11]. Potentilla fulgensWall ex Hook., falls among ethnoveterinary plants as well which is used to regulate the fertility in female cattle by giving whole plant decoction once daily for fifteen days [16].

10. Pharmacological Activities
Pharmacological studies report that Potentilla fulgens possesses antioxidant (in vitro models), antitumor, hypoglycemic and anti-hyperglycemic activities [13-15], antioxidant, anti-inflammatory, antitumorogenic properties.

10.1 Anticariogenic Activity
Initially, Potentilla fulgens is used by tribal people of North-east India to cure teeth and gum problems. Crude methanol extract was found to have good anticariogenic potential. Epigallocatechin gallate was the most effective inhibitor against tested bacterial strains [16]. From Time-kill studies and biofilm formation inhibition assays, catechin (4a–8) epicatechin and Potentilla extracts could be employed as natural antibacterial agents in oral health care products [17].

10.2 Anticancer Activity
Its anti-cancer property was reported by Rosangkima (2010) in which preliminary investigation on some anticancer medicinal plants for cancer therapy conducted in murine ascites Dalton’s lymphoma model. Among them ethanol extract of D. pentagyna showed the most potent antitumor activity, i.e. % ILS ~ 55% and % ILS ~ 49% at a dose of 50 and 100 mg/kg/day, respectively; followed by aqueous extract of P. fulgens showing % ILS ~ 37% at a dose of 50 mg/kg/day. Out of different fraction extracts of D. pentagyna and P. fulgens, better antitumor activity was observed with chloroform extract of D. pentagyna (% ILS ~ 89%) and hexane fraction of P. fulgens (% ILS ~ 37%) at a dose of 50 mg/kg/day, which is due to the presence of alkaloids and flavonoids.

Indian authors determined the effectiveness in antitumor activity among kaempferol (KMP) as flavonoids, ellagic acid (ELA) as polyphenols and methanol extract of the root of P. fulgens (PRE) in Ehrlich ascites tumor (EA) and MCF-7 cancer cells. Phenolic and flavonoid content were 138.8 ± 1.6 mg gallic acid and 40.1 ± 4.6 mg quercetin in per g of the extract, respectively. The extract showed increase in vivo survivability of mice bearing EA cells and loss of cell viability in a dose-dependent manner in MCF-7 cells. Endogenous level of glutathione was depleted significantly in MCF-7 cells after the treatment with PRE only but not with KMP or ELA. Induction of apoptotic cell death and lowering the level of glutathione are highly desirable mode for an anticancer agent. Preliminary investigation on the anti-tumor activity of the methanolic extract of the root of P. fulgens was found to be active in a dose dependent manner [18].

Methanolic (MeOH), butanolic (BuOH) and dichloromethane-MeOH extracts of P. fulgens L. roots showed in-vitro cytocidal activity against various human cancer cell lines viz. Leukemia (THP-1), liver (HEP-2), ovary (OVCAR-5), lung (A-549), prostate (PC-3) and neuroblastoma (SF-295). MeOH extract was found to be most potent and BuOH extract the...
least cytotoxic activity. DCM-MeOH extract showed significant activity against A-549 cancer cell line whereas 6% of control group was given 2% ethanol and the treated groups were given (50-350 mg/kg body weight) of the extract through ip and oral route. After four weeks, animals were sacrificed by cervical dislocation and dissected carefully to remove the liver, kidney and the eye balls of individual group to analyse the activities in Albino-induced diabetic mice shows significant increase in AR activities from normal mice. In liver tissue, AR activity was increased by 63% (p<0.01) in kidney by 67% (p<0.001) and in eye tissue by 58% (p<0.01) as compared to normal mice. At the dose of 250mg/kg via i.p route to the diabetic mice results in AR inhibition, the magnitude varied in a tissue specific manner. The same group also reported tissue specific inhibition of SDH by methanolic extract of Potentilla fulgens L in normal and diabetic mice.

One more study was done by the same authors, to identify the active fraction of P. fulgens with aldose reductase inhibitory potential. Kidney homogenates of normoglycemic and diabetic mice were used as a source of AR enzyme preparation for in vitro analysis. IC50 value (0.152 mg/mL) shows the lowest for Terpenoid/Phenolic (TP) fraction of P.fulgens. Using thin layer chromatography. TP fraction was separated and separated TLC fractions were tested for AR inhibitory activity. F-V had the lowest IC50 value (0.156 mg/mL). Biochemical analysis confirms that the TP fraction contained polyphenolic and flavonoid group which is separated into different fractions by TLC where fraction F-V was found to have better inhibitory activity against AR compared to other TLC fractions.

10.6 Gastroprotective Activity

Gastroprotective activity of ethanolic root extract (EPF) was evaluated on four gastric-ulcer models such as pyloric ligation (PL) ethanol (EtOH), cold restraint stress (CRS) and aspirin (ASP)-induced gastric ulcers. EPF (200–400 mg/kg, p.o.) showed significant protection against acute gastric-ulcer induced by EtOH, PL, and CRS (400 mg/kg, p.o.), but was found to be ineffective against ASP-induced ulcerogens [22]. Alcoholic root extract of Potentilla fulgens (APP), on various gastric ulcer models showed that treatment with APP significantly increased the gastric juice pH, decrease the gastric volume and total acid-pepsin output and significantly reduced the gastric juice cell shedding.

11. Phytochemical Constituents

Potentilla fulgens is rich in polyphenolic and triterpene constituents [23–26]. From the root parts of P. fulgens phytochemical investigation led to the isolation of a novel bioflavanoid potigufeline (Epiapafzelchin-6-o-8” epiafzelchin) along with epicatechin [25]. Two new ursane type triterpenoids, Fulgic acid A [27] and Fulgic acid B were identified and characterized [25].

Choudhary et al [29] had undertaken extensive studies to evaluate the anticancerogenic effects of the plant and search for potent anticancerogenic phenolic molecules. Polyphenolic compounds- 1. Afzelechin 2. Epiafzelchin 3. Epigallocatechin 4. Epigallocatechin gallate 5. Epicatechin 6. Catechin 7. Apigalochetin (4β→8” ) epicatechin 8. Epigallocatechin (4β→8” ) epicatechin 9. Catechin (4α→8”) epicatechin 10. Afzelechin(4α→8”)catechin and 11. Afzelechin (4α→8”) epiafzelchin [29] were isolated from the roots of Potentilla fulgens using semi-preparative HPLC. The structure of the chemical compounds are given below.

10.5 Antidiabetic Activity

Indian author, D. Sify [21] investigated the effective dose of methanolic extract of Potentilla fulgens on Aldose Reductase activities in liver, kidney and eye tissues of normal mice using in vitro and oral routes. Polyal metabolism pathway comprised of two enzymes aldose reductase (AR) and sorbitol dehydrogenase (SDH), which convert glucose to fructose. The pathway is accelerated by elevated cytoplasmic glucose concentrations induced by hyperglycaemia. Swiss albino mice were divided into two groups. The control group was given 2% ethanol and the treated groups were given (50-350 mg/kg body weight) of the extract through ip and oral route. After four weeks, animals were sacrificed by cervical dislocation and dissected carefully to remove the liver, kidney and the eye balls of individual group to analyse the activities in Albino-induced diabetic mice shows significant increase in AR activities from normal mice. In liver tissue, AR activity was increased by 63% (p<0.01) in kidney by 67% (p<0.001) and in eye tissue by 58% (p<0.01) as compared to normal mice. At the dose of 250mg/kg via i.p route to the diabetic mice results in AR inhibition, the magnitude varied in a tissue specific manner. The same group also reported tissue specific inhibition of SDH by methanolic extract of Potentilla fulgens L in normal and diabetic mice.

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From time kill study, adherence study and morphological studies, compounds epigallocatechin, epigallocatechin gallate and epiafzelechin (4β→8) epicatechin were found to exhibit better cariogenic profile than other compounds. Epiafzelechin (4β→8) epicatechin was found to possess comparable anticariogenic effects as of epigallocatechin gallate which suggests that Potentilla fulgens can be considered as a source of anticariogenic agents [1-4] identified various chemical markers in the extracts of P. fulgens roots using NMR, MALDI/TOF/MS, ESI/MS/MS and HPLC/UV. Fourteen marker compounds were detected in the crude methanol extract of P. fulgens by HPLC/UV methods at different wavelengths.

Table 2 Quantization of isolated compounds in methanol extract and roots of P. fulgens

<table>
<thead>
<tr>
<th>Number</th>
<th>Compound</th>
<th>Content % in Methanol-extract</th>
<th>Content % in roots</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Catechin</td>
<td>1.6 ± 0.50</td>
<td>0.40 ± 0.08</td>
</tr>
<tr>
<td>2</td>
<td>Catechin (4α→8) epicatechin</td>
<td>2.1 ± 0.08</td>
<td>0.52 ± 0.08</td>
</tr>
<tr>
<td>3</td>
<td>Alkalol (6→3) catechin</td>
<td>1.5 ± 0.12</td>
<td>0.37 ± 0.09</td>
</tr>
<tr>
<td>4</td>
<td>Alkalol (4β→8) epicatechin</td>
<td>1.32 ± 0.35</td>
<td>0.32 ± 0.15</td>
</tr>
<tr>
<td>5</td>
<td>epicatechin</td>
<td>2.76 ± 0.23</td>
<td>0.52 ± 0.07</td>
</tr>
<tr>
<td>6</td>
<td>Alkalol (5→6) epicatechin</td>
<td>1.46 ± 0.01</td>
<td>0.50 ± 0.07</td>
</tr>
<tr>
<td>7</td>
<td>epicatechin</td>
<td>1.55 ± 0.11</td>
<td>0.50 ± 0.07</td>
</tr>
<tr>
<td>8</td>
<td>epicatechin</td>
<td>1.76 ± 0.05</td>
<td>0.50 ± 0.07</td>
</tr>
<tr>
<td>9</td>
<td>epicatechin</td>
<td>1.53 ± 0.05</td>
<td>0.50 ± 0.07</td>
</tr>
<tr>
<td>10</td>
<td>Eusapic acid</td>
<td>1.21 ± 0.11</td>
<td>0.50 ± 0.07</td>
</tr>
<tr>
<td>11</td>
<td>Fulvic acid A</td>
<td>0.078 ± 0.01</td>
<td>0.019 ± 0.009</td>
</tr>
<tr>
<td>12</td>
<td>Fulvic acid B</td>
<td>0.106 ± 0.02</td>
<td>0.019 ± 0.009</td>
</tr>
<tr>
<td>13</td>
<td>Fulvic acid C</td>
<td>1.33 ± 0.07</td>
<td>0.52 ± 0.07</td>
</tr>
<tr>
<td>14</td>
<td>Ursolic acid</td>
<td>0.075 ± 0.04</td>
<td>0.52 ± 0.07</td>
</tr>
</tbody>
</table>

* Content mean ± SD (n = 3)

Ursolic acid (0.82 ± 0.05%) and epicatechin (0.67 ± 0.03%) were the major compounds in the tested sample of roots [29].

Fig. 6 Structure of (1)Catechin (2)Catechin (4α→8) epicatechin (3) Alkalol (4α→8) catechin (4) Alkalol (4β→8) epicatechin (5) Epicatechin (6) Alkalol (4→8) epicatechin (7) Alkalol (8) Epicatechin (8) epiafzelechin (9) epiafzelechin (10) Eusapic acid (11) Fulvic acid A (12) Fulvic acid B (13) Ursolic acid (14) Corosolic acid quantified using HPLC/UV

Fig. 7 Structure of compounds 2α,3α,20β-trihydroxyru-13-en-28-oic acid, 2a, 3α,20β-trihydroxyru-13-en-28ic and gallic acid [30]

In another study [30], from ethyl acetate extract of P. fulgens compounds, 2α,3α,20β-trihydroxyru-13-en-28-oic acid, 2a,3β,20β-trihydroxyru-13en-28-oic, p-hydroxy benzoaldehyde, gallic acid were isolated which exhibited good antioxidant activity.

Phenolic compounds, quercetin, ellagic acid and kaempferol were reported for the first time in n-butanol fraction of P. fulgens, acts as potential antioxidant and cancer chemo preventive agents [31].

12. Cancer

In pathology, cancer is termed as a malignant and invasive growth or tumor, especially originating in epithelium, tending to recur after excision and to metastasize to other sites. A majority of cancers are caused by changes in the cell’s DNA because of damage due to the environment. The majority of cancers, 90–95% of cases, are due to genetic mutations from environmental factors and the remaining 5–10% is due to inherited genetics [32]. Cancer has a unique combination of genetic changes. Additional changes occur as the cancer continues to grow. Even within the same tumor, different cells may have different genetic changes. The genetic changes that contribute to cancer tend to affect three main types of genes—proto-oncogenes, tumor suppressor genes, and DNA repair genes. These changes are called “drivers” of cancer (NIH, National Cancer Institute, 19.37. Drivers of Cancer. Common cancer types – cancer of Bladder, Breast Cancer, Colorectal Cancer, Kidney (Renal Cell) Cancer, Leukemia, Liver Cancer, Lung Cancer, Lymphoma, Pancreatic Cancer, Prostate Cancer, Skin Cancer, Thyroid Cancer, Uterine Cancer.

13. Ayurvedic Concept of Cancer

Charaka and Sushruta Samhita both described the equivalent of cancer as “granthi” and “arbuda” [33]. Based on the doshas involved “Granthi” and “Arbuda” can be inflammatory or devoid of inflammation [34]. According to the Ayurvedic definition of health, three doshas “Vata, Pitta and Kapha” in body are responsible for disease and the balanced coordination of these doshas in body, mind and consciousness [35]. Tridoshacharudas are usually malignant because all three major body humors lose mutual coordination, resulting in a morbid condition [36]. In Ayurveda, neoplasm can be classified which depends upon various clinical symptoms in relation to tridosha.

Group I: Diseases that can be named as clear malignancies, including arbuda and granthi, such as mammarbuda (sarcomas) and raktarbuda (leukaemia), mukharbuda (oral cancer), and Asadhyya vrama (incurable or malignant ulcers). Group II: Diseases that are not cancers but can be considered probable malignancies, such as ulcers and growths. Examples of these are Mamsaja osththara (growth of lips), Asadhyya galganda (incurable thyroid tumour), Tridosaja gulma, and Asadhyya udara roga, (abdominal tumours like carcinomas of the stomach and liver or lymphomas). Group III: Diseases in which there is a possibility of malignancy, such as visarpa, Asadhyya kamala (incurable jaundice), Asadhyya pradara (untreatable sinussitis) [37].

14. Aim of Cancer Therapy and Cancer Causing Genes

The primary aim of cancer therapy is to act at cellular level which includes (i) inhibiting cancer cells proliferation,(ii) promoting apoptosis of cancer cells, (iii) enforcing the necrosis of tumour and (iv) blocking its metastasis. The secondary aim is to (i) maintain the haemopoietic functions to remain normal and (ii) to promote the reverse transformation from tumour cells to normal cells. There are four main types of gene involved in cell division. Most tumours have faulty copies of more than one of the genes viz., (i) Oncogenes- Ontogenesis were the genes, under normal circumstances starts dividing. When oncogenes are activated they speed up cell’s growth rate. When one of the cell becomes damaged, causing cancer, it is like the accelerator is becoming stuck down (ii) Tumor suppressor genes—This genes make proteins whose normal function is the opposite to that of oncogenesis. P-53 is one of the most important tumor suppressor genes.(iii) DNA repair genes- these are the genes that ensure each strand of genetic information is accurately copied during cell division of the cell cycle. Mutations in DNA repair genes lead to an increase in the
frequency of mutations in other genes such as protooncogenes and tumor suppressor genes. Cells contain many different proteins whose function is to repair the damaged DNA but if the DNA damage occurs to a gene that makes a DNA repair protein, a cell's ability to repair itself will be reduced, and that can allow errors to accumulate in other genes over time.

15. Cancer— a looming threat and its current status in North East India

North-East region of India has different food habits, customs, lifestyle, diverse ethnic groups and type and pattern of tobacco use as compared to the rest of the country. The carcinogenicity of tobacco is attributed to nitrosamines, PAHs, benzene, Benzo(a)pyrene etc. There is extensive use of pesticides in tea gardens in North-East which can lead to widespread occupational and environmental exposures.

ICMR’s National Centre for Disease and Informatics Research released the most recent cancer rates for India, based on data from 27 population-based cancer registries located across the country, including northeast states. The estimate predict 15 lakh new cases of cancer each year in India with breast, lung and cervical cancers topping the list. But the latest data show the highest age-adjusted cancer rates in India are in the Northeast, with Mizoram district in Mizoram for males (271 per 100,000) and Papumpare district in Arunachal Pradesh for females (249 per 100,000). East Khasi Hills ranks third at 211.5 per 100,000 for men in cancer rate in North-East. For certain cancer sites, the highest rates occur in Meghalaya, such as oesophageal cancer in East Khasi Hills for both men (71.2 per 100,00) and women (33.2 per 100,000) as well as hypopharynx (22.2 per 100,00) and larynx (10.8 per 100,000) in men. Tobacco-related cancers have the highest rates in North east (eg. tongue in males; lung, mouth, nasopharynx and oesophagus in both men and women). Cancers of the liver in men and cervix in females are also the other types of cancer which are also estimated to be highest in North-East India.

Table 3  Anticancer plants (Botanical name, parts used, active compounds, origin) (38-40)

<table>
<thead>
<tr>
<th>Anticancer plants (Botanical name)</th>
<th>Parts used</th>
<th>Active compounds</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ficus religiosa</em> (Sacred fig)</td>
<td>Leaf</td>
<td>Flavonoids</td>
<td>India</td>
</tr>
<tr>
<td><em>Cassia fistula</em> (Indian senna)</td>
<td>Leaf</td>
<td>Coumarins</td>
<td>India</td>
</tr>
<tr>
<td><em>Bixa orellana</em> (Achi)</td>
<td>Fruits</td>
<td>Anthocyanins</td>
<td>Brazil</td>
</tr>
<tr>
<td><em>Clitoria ternatea</em> (Blue pea)</td>
<td>Flower</td>
<td>Isoflavonoids</td>
<td>India</td>
</tr>
<tr>
<td><em>Asparagus officinalis</em> (Green bean)</td>
<td>Shoots</td>
<td>Asparagine</td>
<td>China</td>
</tr>
</tbody>
</table>

16. Epigenetics of Cancer

Development of cancer involves alterations of epigenetic processes and their deregulation [41]. In cancer cells, the control of hypermethylation of tumour-suppressor genes on CpG islands is deregulated which results in gene silencing and inactivation of tumour-suppressor genes [42].

There are many forms of cancer which share similar characteristics or genotypes such as insensitivity to signals which inhibit cell growth making their replication limitless. In cancer cells apoptosis is evaded and never induced and angiogenesis is sustained within the tumour tissue allowing survival of cancer cells [43]. In recent years development of new drugs which can inhibit or reverse epigenetic alterations are in process [41]. Some chemically derived epigenetic drugs have been developed and underwent trials such as 5-aza-2'-deoxycytidine (decitbine; Dacogen) which are both DNMTi [44] and HDACi such as suberoyanilidehydroxamic acid (SAHA, Vorinostat, Zolinza) and FK228 (Romidespin, Istodax). But, it is difficult to get a chemically derived drug which is non-toxic to normal cells and is specific to cytotoxicity of cancer cells. Therefore, research and development into naturally derived compounds to be used for anticancer treatment is becoming high in demand with a focus on those derived from plant species and their natural products.

17. Molecular Mechanisms of Cancer

Cell genotypes of cancer are a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth; self-sufficiency in growth signals, insensitivity to growth-inhibitory (anti-growth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis and tissue invasion with metastasis. Environmental as well as endogenous DNA-damaging agents and genetic instability drive tumor progression by generating mutations in two types of genes, oncogenes and tumor suppressor genes, providing cancer cells with selective growth advantage and thereby leading to the clonal outgrowth of a tumor. At first proto-oncogenes can be activated by translocations. For e.g. Burkitt’s Lymphoma results from translocation of the c-myc protooncogene from chromosomes 2,14 or 22. Secondy proto-oncogenes can be activated by point mutations. For e.g. in a large variety of malignant neoplasms it is found that point mutations of genes coding for guanosine-triphosphate binders proteins such as H-Ras, N-ras or G proteins can be oncogenic. Third mutations that inactivate a gene can result in tumors if the product of the gene normally constrains cellular proliferation [45].

Fig. 9 Flowchart depicting a simplified scheme of the molecular basis of cancer

18. Cancer Prevention

Around 30-50% of all cancer cases are avertable. Prevention offers the most cost-effective long-term strategy for the control of cancer. The preventive measures should be taken from: Tobacco- Tobacco smoking: causes cancers of the lung, oesophagus, larynx (voice box), mouth, throat, kidney, bladder, pancreas, stomach and cervix.

Physical inactivity, dietary factors, obesity and being overweight-Dietary modification is an important approach to cancer control. There is a link between overweight and obesity to many types of cancer such as oesophagus, colorectum, breast, endometrium and kidney. Diets rich in fruits and vegetables may have an independent protective effect against many cancers. Regular physical activity, maintenance of healthy body weight, healthy diet considerably reduce cancer risk.

Alcohol- Alcohol use is a risk factor for many cancer types including cancer of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and breast.

Infections- Approximately 15% of all cancers was attributable to infectious agents such as Helicobacter pylori, human papilloma virus (HPV), hepatitis B and C, and Epstein-Barr virus. Vaccines are available for hepatitis B virus and some types of HPV and can reduce the risk of liver and cervical cancers, respectively.


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Environmental pollution - Pollution of air, water and soil with carcinogenic chemicals contributes to the cancer burden to differing degrees depending on the geographical settings.

Occupational Cancers - Occupational cancers are concentrated among specific groups of the working population, for whom the risk of developing a particular form of cancer may be much higher than for the general population. Occupational carcinogens are causally related to lung cancer, mesothelioma, and non-melanoma skin cancer.

Radiation - Exposure to all types of ionizing radiation, from both natural and man-made sources, increases the risk of various types of malignancy including leukemia and a number of solid tumours.

19. Chemoprevention of Cancer: A Rational and Appealing Strategy

Cancer chemoprevention is the use of natural, synthetic, or biological chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer [46]. Cancer chemopreventive agents can be classified in four major categories: hormonal, medications, diet-related agents, and vaccines. Primary chemopreventive agents refer to the use of an agent that prevents carcinogenesis in healthy individuals. At higher risk, the other hand secondary chemoprevention refers to preventing the full transition to malignancy in a patient who already has developed a premalignant lesion. Chemopreventive agents are subdivided into two main categories: (i) blocking agents, which inhibit the initiation step by preventing carcinogenization and (ii) suppressing agents, which inhibit malignant cell proliferation during promotion and progression steps of carcinogenesis [47, 48]. Two major mechanisms of cancer prevention are antimitogenesis which includes the inhibition of the uptake of carcinogens, the formation/activation of carcinogens, the deactivation/detoxification of carcinogens, the blocking of carcinogen uptake, the formation/activation of carcinogens, the prevention are antimutagenesis which include inhibition of malignant cell proliferation during promotion and progression steps of carcinogenesis.

20. Medicinal Plants and Cancer

The active substances or secondary metabolites found in a large number of medicinal plants which affect the uncontrolled cell division of many plants are used for the treatment of cancer [51]. Chemotherapy is routinely used for the treatment of cancer. An cancer cell loses some of the regulatory functions present in normal cells, they continue to divide when normal cells do not which makes cancer cells susceptible to chemotherapeutic drugs [52]. A large collection of useful chemotherapeutic agents have already been established. However, chemotherapeutic treatments are not devoid of their own intrinsic problems. Various kinds of toxicities may occur as a result of chemotherapeutic treatments. For e.g. doxorubicin causes cardiac toxicity [53-55] renal toxicity [56] and myelotoxicity [57]. There are many significant plants well known for their multiple aspects of medicinal influence e.g. Taxus brevifolia (Taxaceae), Catharanthus roseus (Apocynaceae), Pedicularis elatum (Berberidaceae), Camptotheca acuminata (Cornaceae), and Cephalotaxus harringtonia (Cephalotaxaceae) [51]. Among them Potentilla fulgens is one of them. The National Cancer Institute (NCI) screened approximately 35,000 plant species for potential anticancer activities. Among them, about 3,000 plant species have demonstrated reproducible anticancer activity.


Toxicity of chemotherapeutic drugs sometimes creates significant problem in the treatment of cancer using allopathy or established medicines. Various therapeutic agents have been progressively promoting the development of cancer many of which use plant-derived products because plant derived products have less cytotoxicity than therapeutic drugs. There are four classes of derived anticancer agents the vinca alkaloids (vinblastine, vincristine and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel) and the camptothecins (camptothecin and topotecan). The anticancer characteristics of a number of plants are still being actively researched and some have shown promising results. Among them Potentilla fulgens, which is found in Northeast part of India is still less known by people but have many potential medicinal values and anticancer characteristics.

22. Role of Plant phytochemicals on Cancer

Due to the adverse effects produced by chemotherapy and radiation therapy, plant derived phytochemicals possessing anticancer activities have received considerable attention in recent years. The phytochemicals which are derived from traditional medicinal plants have been found to possess anticancer and chemo protective effects. Plant phytochemicals are in demand as they are safer for long term use in cancer patients. Due to the effective antioxidant activity they provide nutrition and reduce the side effects of conventional cancer therapy. Antioxidant activities of the methanol extract, fractions and isolated compounds from the roots of Potentilla fulgens Lodd. were evaluated by three in vitro experiments, namely, ABTS, DPHI, and FRAP assays. PF-2 was characterized as a new bi-flavanoid and designated as Potfulgene on the basis of NMR and mass spectrum, whereas PF-1 was identified as epicatechin. The antioxidant activity of new biflavanoid (Potfulgene) was found to be higher than that of epicatechin with ABTS, DPHI and FRAP assays. Since Potentilla fulgens have antioxidant activity it is strongly associated with reduced risk of developing chronic diseases such as cancer as the phytochemical extracts from it exhibits strong antioxidant activity. The United States National Cancer Institute (NCI) instigated and fund a major screening programme, in which an intensive survey of plants, microorganism and marine animals for antitumour activity was investigated. Genistein, (4, 5, 7-trihydroxy isoflavone) which is a soybean phytochemical inhibit the growth of transplantable human prostate carcinoma [59]. Andrographolide is a potential cancer therapeutic agent isolated from Andrographis paniculata [60]. An alcoholic extract of Biorhythms sentium for antitumour activity could inhibit the solid tumor deve acites (DLA) cells and increase the life span of mice bearing Ehrlich ascites carcinoma (EAC) tumors [61]. The natural antioxidant gallic acid (GA) isolated from the fruits of an Indonesian medicinal Plant, Phaleria macrocarpa was proved to be a potent anticancer compound [62]. From ethyl acetate extract of P.fulgens gallic acid were isolated which acts as potential antioxidative and cancer chemopreventive agents [65].

23. Toxicity

Toxicity of chemotherapeutic drugs sometimes creates significant problem in the treatment of cancer using allopathy or established medicines. Various therapeutic agents have been progressively promoting the development of cancer many of which use plant-derived products because plant derived products have less cytotoxicity than therapeutic drugs. There are four classes of derived anticancer agents the vinca alkaloids (vinblastine, vincristine and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel) and the camptothecins (camptothecin and topotecan). The anticancer characteristics of a number of plants are still being actively researched and some have shown promising results. Among them Potentilla fulgens, which is found in Northeast part of India is still less known by people but have many potential medicinal values and anticancer characteristics.

24. Main Chemical Constituents of P. fulgens with Anticancer Properties

Compounds which have been identified and extracted from P. fulgens for their anticancer properties include polyphenols, flavonoids.

20.1 Polyphenols

Flavonoids, tannins, curcumin, resveratrol and galacteacines are the polyphenolic compounds which are considered to be anticancer compounds [65]. The cytotoxicity of polyphenols on a range of cancer cells has been demonstrated as well as their antioxidant properties determined [66]. Polyphenols have shown promising properties anticancer properties which can be utilized. The mechanism behind which polyphenols are thought to carry out apoptosis initiation is through regulating the mobilization of copper ions which are bound to chromatin inducing DNA fragmentation [65]. Polyphenols also show their ability to interfere with proteins which are present in cancer cells and promoting their growth. Cancer agents is altered through the polyphenol regulating acetylation, methylation or phosphorylation by direct binding of ions [68].

20.2 Flavonoids

Flavonoids are from the polyphenolic compounds and it constitute a large family of plant secondary metabolites [69]. Flavonoids demonstrate cytotoxicity on cancer cells and to have high free radical scavenging activity [66]. Purified flavonoids show show anticancer activities against various cancers including: hepatoma (Hep-G2), cervical carcinoma (Hela) and breast cancer (MCF-7) [70]. Kaempferol (KMP) as flavonoids, ellagic acid (ELA) as polyphenols and methanolic extract of the root of P. fulgens (PRE)
shows effectiveness in antitumor activity in Ehrlich ascites tumor (EA) and MCF-7 (breast) cancer cells.

25. Plant Derived Bioactive Compounds as Leads to Anti-Cancer Drugs

Traditional medicines when compared to other sources of drug discoveries and other therapeutic drugs had contributed many novel therapeutic compounds for prevention and curative medicine. The secondary metabolites like polyphenols, terpenes, and alkaloids have been reported to possess antitumor and anticancer properties in many studies [71]. These secondary metabolites are also found to be present in different fractions of Potentilla fulgens root extract which shows P. fulgens as a potent source of anticancer agent also there is an enormous prospect for using it as a novel candidate and lead molecule in food and medicine industry as a natural alternative medicine. Traditional medicine derived from herbal medicinal plants and knowledge of Ayurveda help in the discovery of new drug leads with high activity and low toxicity for cancer therapy which focuses on the isolation of bioactive lead compounds, chemical modifications and improving pharmacological activity [72].

Plant-derived anti-cancerous drugs are divided into four major structural classifications viz., Vinca alkaloids, Epi-podophyllotoxin lignans, Taxane diterpenoids and Camptothecin quinoline alkaloid derivatives. Some anticancerous drugs that have been identified and reported are - Vinblastine (VLB) and Vincristine (VCR), Podophyllotoxin, Taxane, Camptothecin (CPT), Berberine, Betulonic acid, Berberine, Betalapachone, Betulinic acid, Brucatin, Colchicine(Nirmala et al., 2011). Discovery of new drugs is time consuming also laborious. So certain natural products and their analogs can be enhanced for anticancer activity by synthesizing new derivatives based on active pharmacophore models. The isolated lead molecules derived from medicinal plants are used as an alternative medicine for treating neoplastic cells [73].

<table>
<thead>
<tr>
<th>Drug</th>
<th>2D Chemical structure (adapted from Pubchem database)</th>
<th>Medicinal Use</th>
<th>Mechanism of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinblastine</td>
<td></td>
<td>east, lymphoma, breast, lung, and solid cancers</td>
<td>Inhibits cell proliferation by acts as mitotic block</td>
<td>[74]</td>
</tr>
<tr>
<td>Vincristine</td>
<td></td>
<td>leukemia</td>
<td>Inhibits cell proliferation by acts as mitotic block</td>
<td>[74]</td>
</tr>
<tr>
<td>Taxol</td>
<td>stinancer agent</td>
<td>Anti-mitotic agent</td>
<td>[75]</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
<td>east and lung cancer</td>
<td>Prevents mitosis by binding to microtubules</td>
<td>[76]</td>
</tr>
<tr>
<td>Topotecan</td>
<td>ovarian, lung and prostate cancer</td>
<td>Through inhibition of DNA topoisomerase I</td>
<td>[77]</td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>colorectal and lung cancer</td>
<td>Through inhibition of DNA topoisomerase I</td>
<td>[78]</td>
<td></td>
</tr>
</tbody>
</table>

| Betulinol | Normal cells and tissue are relatively resistant to Betulinic acid | They trigger the mitochondrial pathway of apoptosis which causes cancer cell death | [79] |
| Colchicine | Betulinic acid | Betulonic acid | [80] |
| Beta-lapachone | Betulinic acid | Betulonic acid | [81] |
| 4-Lipomanol | Breast cancer, prostate cancer, lung cancer, and promyelocytic leukemia | Inhibition of topoisomerase I and II | [82] |
| Silvestrol | Prostate, breast and lung cancer | Apoptosis/mitochondrial pathway was involved in triggering extrinsic pathway of programmed cell death of tumor cells | [83] |
| Salvicine | Malignant tumors | Inhibition of topoisomerase II | [84] |
| Emodin | Lung, liver, ovarian and blood cancer | Apoptosis of cancer cells by several pathways | [85, 86] |

26. Prospects

Healing with medicinal plants is as old as mankind itself. In recent time, there is a shift towards herbal cures. Currently medicinal plants are gaining significance due to the various phytochemicals present in them which helps in maintaining good health and used in various therapeutic treatments. Systematic evaluation of its anticancer efficacy was limited so more extensive studies using various analytical techniques have to be performed. It is necessary to investigate the effects of different fractions of Potentilla fulgens root extract in conventional medicines. Furthermore, investigation has to be done at molecular level to understand its mechanism of action. In depth phytochemical studies as well as pharmacological profile based on in vivo and in vitro and on clinical trials comparing the metabolic pattern is insufficient and further study should be done on the discovery of the exact mode of action of the various extracts prepared from Potentilla, the isolated pure compounds and potential combinations to utilize them pharmacologically.

27. Conclusion

Potentilla fulgens is a significant medicinal herb which contains polyphenols in its stem, leaves and roots parts. High amount of tannins and a lesser extent of triterpenes are present in Potentilla fulgens which explained the pharmacological effects to a vast extent. Polyphenols, flavonoids, tannins are the chemical constituents which results in its anti-
hyperglycemic, anti hyperlipidemic, anti tumor and antioxidant property. Potentilla fulgens extracts have been used for treating diarrhea, hepatitis and rheumatism. Though Potentilla fulgens have served as an exemplary source of traditional medicine, it remains a challenge to provide a more efficient cheap medications for rural masses from this plant. Current pharmacological modalities for treating diabetes, diarrhea, hepatitis are not so much ideal and effective because of their side effects, reduction of response after prolonged use and also expensive as well. So, the traditional way of using Potentilla fulgens and the plant extracts shows good remedy for a variety of ailments including cancer due to the presence of rich amount of phytochemicals in them. If all these studies are carried out in depth, this plant can be a very potent source for developing plant based anti-cancer remedy like taxol or vinca alkaloids.

References


