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Anticancer and anti-inflammatory potential of some important medicinal plants of Kashmir valley, India

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Abstract

Cancer is second leading disease after heart related disease which causes death and is marked by uncontrolled growth and proliferation of cells. There are round about 100 types of cancers, each classified by type of cells they initially affect. Vast number of the plants from valley are claimed to possess the anticancer, anti-inflammatory and analgesic properties and are used extensively by the people not only for inflammation but as analgesic, antispasmodics and antimicrobials etc. Medicinal plants are playing a major role to cure many diseases related with the inflammation. As we know prolonged inflammation can also be a cause for development of cancer. When vascular tissues show systematic response it is known as inflammation. Therefore, the researchers today are emphasizing on various plant constituents their evaluation and characterisation that have a role to play against many diseases. In this current review, an endeavour has been created to give a list of some important medicinal plants that are found in Kashmir valley having anticancer as well as anti-inflammatory properties.

Keywords: Anti-inflammation, antispasmodics, proliferation, analgesic

1. Introduction

Pathogen, chemical agents and autoimmune responses are responsible for inflammation and under the influence of an inflammatory factor, some intracellular biochemical substances are released from cells. Monocytes and macrophages produce cytokines. The most fundamental role of cytokines in inflammatory response is to activate cells involved in the inflammation (neutrophils, macrophages, and mast cells), during which the body protects itself against harmful stimuli^[1] and also to induce the synthesis of prostaglandins and the synthesis of the C-reactive proteins is affected. Among cytokines one can differentiate between pro-inflammatory (interleukins IL-1, IL-6, IL-8, IL-17, IL-18, α and β interferon, and the tumor necrosis factor and anti-inflammatory ones (e.g. IL-4 etc)^[1, 2]. Anti-inflammatory action of medicinal plant material affects various stages of inflammation process thus inhibiting formation of cytokines and eicosanoids, preventing the harmful reaction cascades from starting, and diminish skin flare, itching or excessive exfoliation^[3]. As we know Kashmir is known from long having a tradition of treating with herbal drugs. There has been continuous growing tradition of herbal treatment and both Unani and Ayurvedic systems of medicine have played a major role in health care of this region^[4]. It has been assumed that just as our body has mechanism to extract multiple components from food, it is also designed to do same from plants material. The prescription which is made from herbal mixture form the basis, the multiple ingredients in traditional prescription may include some plant material which have been selected to address the particular site of pathology, other to stimulate a more generalised immune response, still others to offset side effects in some of ingredients and others to cellular uptake is increased^[5]. The complex approach of pharmacology depends on a concept of synergistic activity of multiple components in a traditional formula. The high altitude Kashmir valley has about two thousand plant species and many the plants in form of powder, paste and decoctions are used by rural people for curing of various diseases. Plants are good source of generic products used in medicine^[4, 5].

1.1 Inflammation

Defence system of the body is Inflammation and important immune response that helps the body to withstand and survive during infection/injury and maintains tissue homeostasis in noxious and other harmful conditions which includes swelling of body parts, painful, and often hot, (mainly as a reaction to injury or infection^[6]. It is a normal response to any harmful stimulus that affects the host and may vary from localized to a generalized response. We can say that "Inflammation is the result of complex reactions of the body to various infections

upon tissue injury [7]. It has a main role in healing, corrective processes, but it can have an antagonistic role also. But in some conditions proven not to be responsive and a chronic stage develops that may cause the lost the life of an individual and in many cases leads to serious results that include the following inflammatory disorders like psoriasis, rheumatoid arthritis, osteoarthritis, retinitis, multiple sclerosis, and atherosclerosis. To overcome these problems a large number of different kind of safe and more effective anti inflammatory agents are available and many more drugs are under process. So these agents which are helpful to reduce the inflammatory response are called anti-inflammatory agent [8].

1.1.1 Types of inflammation

Inflammation is a defined as large number of sequenced events that occurs in response to harmful or damage causing stimuli and infection or trauma. Inflammation responses are mainly diagnosed by the following characteristics like redness, swollen joints and joint pain, its stiffness and loss of joint function. It is mainly of two types. They are
 Acute inflammation: It is characterised by pain, edema, erythraemia triggering infiltration of serum and WBC to tissue being affected, later by oozing of plasma proteins and fluids followed by migration of WBC's, important of which is

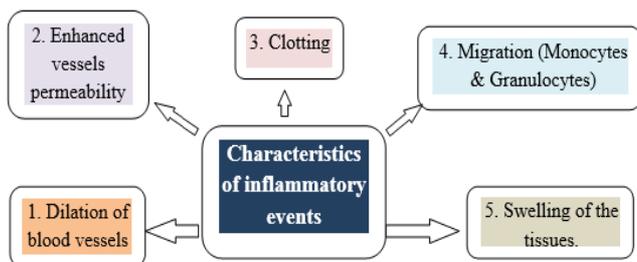
migration of neutrophils to the affected area. Acute inflammation usually occurs within short period of time or at most some hours after tissue injury, and has symptoms like redness and oedema [7]. This type of acute inflammatory response is very useful for the defence mechanism which is aimed at killing of different bacteria, virus and parasites while still facilitating wound repairs [9].

Chronic inflammation: Progressive shift of cells characterised by tearing down and alleviation of tissue cells simultaneously [10]. Chronic inflammation has more prolonged time. The chronic inflammation leads to the development of the different degenerative diseases such as RA, Atherosclerosis, Alzheimer, Asthma, Gout, IBD, aging and other neurodegenerative disorders, it has also has been implicated as part of loss of muscle that may be seen along with progress of age [7]. All of which are associated with immunopathological that appears to play a key role in the onset of the condition. Inflammatory changes are responsible for producing different biologically active substances from polymorphonuclear leucocytes and lysosomal enzymes. Some vascular effects are mediated by kinnins, prostaglandins and histamines released by mast cells [7, 9]. Difference between the chronic and acute inflammation is given in table 1.

Table 1: Comparison between chronic and acute inflammation

	chronic	Acute
Causative agent	Viral infection, continuous foreign bodies, Due to non-degradable pathogen causes persistant inflammation and autoimmune reactions	Tissue injuries and pathogens
Cells	Monocytes (macrophages, lymphocytes), fibroblasts	Neutrophils basophils, and eosinophils and mononuclear cells
Mediators	IFN- and cytokines, ROS, hydrolytic enzymes	Eicosanoids, vasoactive amines
Effect	Delayed	Immediate
Time duration	Months or years	Few days
Outcomes	Destruction of tissue, necrosis	Abscess formation, resolution

Table 2: The characteristic events that occur during inflammation are depicted



1.1.2 Inflammatory disorders

The immune system of our body is often affected by inflammatory disorders, in sympathies as well as in allergic reactions. Non immune diseases like cancer, ischemic heart diseases and arthrosclerosis have casual origins in inflammation. Disorders associated with inflammation include

- Hypersensitivities
- Intersititial cystitis
- Mastocytosis
- Rheumatic fever
- Transplant rejection
- Acne vulgaris
- Autoimmune disease
- Colitis
- Inflammatory bowel diseases
- Mast cell activation syndrome
- Otitis
- Sarcoidosis
- Vasculitis
- Asthma
- Celiac disease
- Chronic prostatitis

2. Cancer

Billions of money is invested in research of cancer and yet we do not come to a conclusion what it [11]. 2-3% of annual deaths worldwide are due to cancer killing about 3500 million people annually worldwide. Several chemo protective agents are employed in treatment of cancer, but they also have toxic effects on body that prevents to use them [12]. Solid tumours are usually part of normal tissues, and under optimal conditions, can attack neighbouring tissues or pass out through the connective system to colonise distant sites in the body. These secondary tumours – metastases – are cause for almost 90% of the deaths caused by cancer. This capability of tumour cells to attack and metastasize is the final of the six hallmarks of cancer. Metastasis enables tumours to survive and grow in new environments where there are no restrictions of space or nutrients [13]. Gene mutation is one of major cause of cancer, these mutations may occur after birth or are inherited a number of forces can cause these gene mutations such as alcohol, smoking, unbalanced diet, pollution (pollutants), hormones, chronic inflammation and infection. Fig 1 shows global distribution of cancer causes throughout the world and the most common causes leading to cancer.

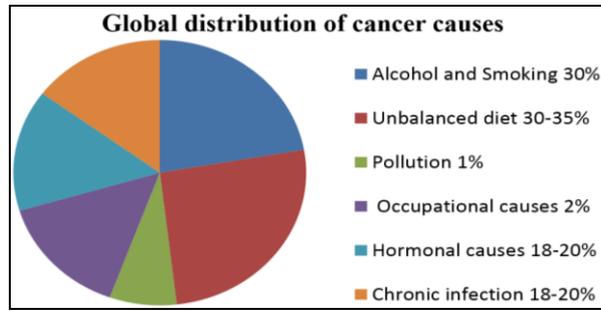


Fig 1

Table 3: Different hallmarks of cancer due to mutation which disrupts the normal behaviour of cells. The 6 hallmarks of heterotypic model (currently accepted model) can be described as

1) Immortality	Cells divide continue and replicate
2) Go'signals	Growth response factors are produced from Oncogenes
3) Stop' signals	Anti-growth signals from tumour suppressor genes
4) Resistance to cell death	Apoptosis
5) Angiogenesis	Induction/formation of new blood vessel growth
6) Metastasis	Spread of tumour to other sites

However, metastatic tumours display additional unique cellular features, which enable them to change and adapt to their new environments. The precise mechanism of all these is a complex process and still the subject of intense research, but involves a common strategy to physically lodge the cancer cells in the new site by causing the activation of extracellular

proteases [14].

Table describes the stages of metastasis? The migration of cancer cells from the primary location to a distant site is a complex biological process that involves changes at the molecular, cellular and physical level.

Table 4: The invasion and metastasis cascade typically involves the following stages

Local invasion	The small in situ tumour breaks through the basement membrane barrier
Intravasation	The tumour cells move through the walls of the capillaries or lymphatics into the circulatory system (invasiveness and cell motility)
Transport	Cancer cells travel through the blood or lymph until they anchor to a solid supporting tissue.
Extravasation	This step of migration is essentially similar to intravasation, in which eventually move into the tissues they are lodged in, typically lungs, brain or liver. The main difference is that the direction of movement is reversed.
Micrometastasis	The cancer cells are now able to reactivate the cell proliferation pathways
Colonisation	This is the most complex and challenging stage mainly because the new environment may not always provide the necessary survival and proliferation factors needed for growth. Most cancer cells usually die or survive for long periods as micrometastases (which are much harder to detect).

Yet cancers occur in 33% of the human population on average. Does this mean that tumours must somehow have a higher mutation rate than predicted with the signalling pathways? One school of thought argues that perhaps mutations in the 'caretaker' or guardian genes are responsible for this increased mutability. The most compelling evidence for this argument comes from mutations in the p53 tumour suppressor protein, found in the vast majority of human tumours. It plays a pivotal role in determining cell fate in response to DNA damage; should cell cycle arrest and repair pathways be switched on or should the cell be allowed to die by apoptosis? Moreover, other proteins involved in sensing and repair have also found to be functionally lost in different cancers [14]. According to the World Health Organization (WHO), about three quarters of the world's population currently use plant products and other forms of traditional plant based medicines to treat many different diseases. Simplifying and dissecting the pathways involved in each of these signalling pathways have been vital in understanding this process. On the other hand, the danger of simplification is that it reflects little of the biological reality of cancer progression in human patients in vivo. Empirical evidence in vitro have often failed to match the results from in vivo studies. This has led to profound rethinking and of how we study cancer experimentally. Systems level approaches (heterotypic organ cultures in vitro, refined animal models

and even translational medicine) will help us define comprehensive maps in cancer signalling networks New technologies have enabled us to identify epigenetic modifiers (agents that modify the expression without changing the DNA sequence – such as microRNAs) located either within the cancer cell or elsewhere in the body. It is most likely that in nearer future, diagnosis of all cancers will rely on routine expression profile analysis of the array of underlying genetic mutations and/or their epigenetic modifiers. Emerging technologies may also help us understand the complex interactions between various components of these complex signalling networks. Plants based treatment has been employed for treatment of various types of diseases of human beings and animals since time long. They maintain the health of individuals, and also cure diseases, including cancer without causing toxicity [14, 15]. Also different food eating habits has a vital role in prevention of cancer because these food items contain different ingredients or constituents which help to fight cancerous agents and different radicals, different some food items like vegetables, Fruits etc reduce the risk of cancer while on the other hand smoking, Alcohol consumption, Salted foods etc increase risk of causing cancer. (Table 5) Many studies suggest that a phytochemical rich diet which includes colourful fruits and vegetables may reduce the risk of human cancer diseases.

Table 5: Different some food items like vegetables, Fruits etc which help to fight cancerous agents and different radicals

Type	Decreases Risk	Increases Risk	Preventable by Diet
Lung	Vegetables, fruits	Smoking	33-50%
Stomach	Vegetables, fruits	Salt, salted foods	65-75%
Colon/Rectum	Vegetables, fruits, Activity	Alcohol, Smoking	66-75%
Mouth/throat	Vegetables	Smoking	33-50%
Liver	Vegetables, fruits	Alcohol, contaminated food	33-66%
Cervix	Vegetables, fruits	Smoking	10-20%
Esophagus	Vegetables	Smoking, alcohol	50-75%
Prostrate	Vegetables, fruits	Meat fat, dairy fat	10-20%
Bladder	Vegetables, fruits	Smoking, coffee	10-20%

World cancer research fund, American institute of cancer Research

3. List of some medicinal plants in kashmir valley having anti-cancer, anti-inflammatory

There are about 2000 plants species that are found in Kashmir and many among them having anticancer potential. The molecules extracted from these plants have shown wonders. such molecules are present in large numbers in different plants but needs extensive studies. Plant polyphenols are natural antioxidants and most of their activities are due to their antioxidant action [16, 17]. This is due to their ability to scavenge interiorly generated ROS or those radicals which are formed by various xenobiotics, radiations etc. Many studies suggest that a phytochemical rich diet which includes colorful fruits and vegetables may reduce the risk of human cancer diseases. Phenolic compounds (flavonoids or polyphenols) in plant foods have numerous biological activities including antioxidant properties. Dietary intake of natural Phenolic antioxidant has been suggested to contribute to the prevention of inflammation and cancer [17, 18].

Kashmir has got huge flora of such medicinal plant. There are different ways of using some plants such as *Allium sativum* (Rohun), *Achillea millefolium* (Pehl-ghasa), *Nepeta cataria* (Gande-soi), *Artemisia absinthium* (Tethwen), etc. as antibiotics. The valley is full in unique flora of medicinal plants being different from those in the rest of the country and other parts of the world. Some of the most important medicinal plants of Kashmir are *Artemisia spp.*, *Arnebia benthamii*, *Allium cepa L.*, *Allium sativum*, *Aconitum heterophyllum*, *Plantago lanceolata*, *Datura stramonium*, *Inula racemosa*, *Cannabis sativa L.*, *Podophyllum hexandrum*,

Hyoscyamus niger, *Nepeta cataria*, *Urtica dioica* Linn etc. Discovery of drugs from medicinal plants has played crucial role in treatment and prevention of cancer, four major types of anticancer agents which are under trial are Taxanes, vinca alkaloids, epipodophyllotoxins and camptothecins [19]. The high altitude Kashmir valley has about 2000 plant species and many the plant species in form of powder, paste and decoctions are used by rural people for treatment of various diseases. Plants are good source of natural products used in medicine. Generally, populations that consume a good level of natural products have less chances of cancer. There is great interest in finding for plants to be used in cancer prevention and treatment. For this reason different extracts from different plants have been thoroughly studied. Search for new anti-inflammatory substances from various sources as novel anti-inflammatory chemotherapeutic agent. Plants have a wide availability of bioactive compounds making them a highly reliable source of medicines. Majority of these plants are rich with constituents having anti-inflammatory properties which protect against assailant agents, generally microorganisms [18, 20]. Practitioners use different plant extracts of plant formulations for inflammation, analgesics and antirheumatic action with great success [20].

4. This study is focused on screening of traditionally used medicinal plants for anticancer and anti-inflammatory effects. Some of the medicinal plants of Kashmir valley having anticancer and anti-inflammatory properties are

Name	Family	Local name	Part used	Uses	Reference
<i>Abies pindrow</i>	Pinaceae	Sal	Bark	Anti inflammatory anti Rheumatism	[21]
<i>Achillea millefolium</i>	Asteraceae	Berguer	Leaves	Head ache, Tooth ache, anti inflammation	[5, 18, 22]
<i>Adiantum cappilus veneris</i>	Adiantaceae	Gautheer	Whole plant	Anti inflammatory and Analgesic	[23]
<i>Aconitum heterophyllum</i>	Ranunculaceae	Patis, paewakh	Root	Anti cancer (Lung, Pancreatic MiaPica, Colon HCT-116)	[5, 13, 24]
<i>Acorus calamus</i>	Acoraceae	Via-gander	Rhizome	Swellings, Joint pain & anti inflammatory	[5, 16, 23, 40, 43]
<i>Anemone obtusiloba</i>	Ranunculaceae	Srub	Seeds	Analgesic, anti inflammation & Rheumatism	[18, 25, 26]
<i>Artemisia meritima L</i>	Compositae	murin	Root	Anticancer (Breast MCF-7.)	[13]
<i>Asparagus officinalis</i>	Liliaceae	Parglas	whole plant, roots	Toothache, Rheumatism, Female infertility	[5, 18, 25, 26, 41]
<i>Atropa belladonna</i>	Solanaceae	Sagangur	Leaves	Analgesic (joint pain)	[23]
<i>Basella Alba Linn</i>	Basellaceae	Poi	Leaves	Analgesic & anti inflammation	[27, 44]
<i>Berberis lycium Royale</i>	Berberidaceae	Kawdach	Leaves	Anticancer Breast and pancreatic	[13]
<i>Bergenia ligulata</i>	Saxifragaceae	Pashanabhed	Leaves	Analgesic & Antiseptic(stomach ache)	[18, 23, 27]
<i>Brassica rapa</i>	Brasicaceae	Tilgogul	Seeds	Analgesic (Abdominal pain)	[23]
<i>Cannabis sativa</i>	Cannabaceae	Bhang	Leaves	Anti inflammatory, Diarrhea and mensuration problems	[5, 18]
<i>Crocus sativus L (cashmmerianus)</i>	Iridaceae	zaffran	Flowers (petal)	Anti inflammatory	[27]
<i>Cascuta reflexa</i>	Cuscutaceae	Kukliporte	Whole plant	Analgesic)Joint pain, anti inflammatory	[16, 18]
<i>Cynodon dactylon</i>	Poaceae	Daraunm	wholeplant	anti-helminthic, anti-diuretic, anti-inflammatory, hepatoprotective	[29]
<i>Dioscorea deltoidea Wall</i>	Dioscoreaceae	Krinch	Tuber	Anti-inflammatory	[5, 16]
<i>Datura stramonium</i>	Solanaceae	Datur	Leaves	Analgesic (Rheumatic pain)	[17, 23, 30]
<i>Euonymus hemiltonianus</i>	Celastraceae	Sheelkul	Berries	Analgesic and Anticancer (Lung, breast, colon and pancreatic)	[13]

<i>Euphorbia wallichii</i>	Euphorbiaceae	Heerab	Root	Anticancer (breast, colon and pancreatic)	[13]
<i>Euphorbia helioscopia</i>	Euphorbiaceae	Gursochal	Leaves	Anti-cancer, analgesic	[16, 23,42]
<i>Ficus cirica L</i>	Moraceae	Anjeer	Fruit	Analgesic and Anticancer (Lung, breast, colon and pancreatic)	[13]
<i>Foeniculum vulgare</i>	Apiaceae	Badiyan	seed	indigestion	[23]
<i>Gentiana kurroo Royale</i>	Gentianaceae	kadu	Whole plant	Anti-inflammatory and immunomodulatory	[32]
<i>Hyoscyamus niger</i>	Solanaceae	Bazarbang	Seed	Tooth ache & anti inflammatory	[16,23]
<i>Impatiens glandulifera</i>	Balsaminaceae	Trul	Leaves	Analgesic (Joint pain) & anticancer	[5, 27,30]
<i>Iris nepalensis</i>	Iridaceae	Sonzal	Stem	Analgesic (Joint pain)	[23]
<i>Juniperus communis</i>	Curpessaceae	Bithur	Leaves	Rheumatism & anti-inflammatory properties	[16, 27, 31]
<i>Iris kashmiriana</i>	Iridaceae	Mazarmund	Whole plant	Analgesic (Joint pain) & anti inflammatory	[4, 5, 32]
<i>Ligustrum lucidum L</i>	Oleaceae	Privat kul	Barriers	Anticancer (Breast and pancreatic)	[5]
<i>Mentha arvensis</i>	Lamiaceae	Pudina	Whole plant	Analgesic (Abdominal pain)	[23]
<i>Oxalis corniculata</i>	Oxalidaceae	Amrul	Leaves	Anti-inflammation	[16, 23, 26]
<i>Portulaca</i>	Portulacaceae	Nuner	Whole plant	Anti-inflammation	[23]
<i>Potentilla nepalensis</i>	Rosaceae	Ratanjot	Leaves	Anti-inflammatory and Analgesic	[23, 18]
<i>Prunellavulgaris</i>	Lamiaceae	Kulwauth	Flower	Headache, Fever, muscular pain	[5, 33, 34]
<i>Rumex acetosa</i>	Fabaceae	Abej	Whole plant	Stomach disorders	[5]
<i>Saussurea coctus</i>	Astraceae	Kruth	Root	Anti-inflammatory & Analgesic (Joint pain)	[23]
<i>Salix wallichiana</i>	Salicaceae	Danthiveer	Leaves	Anti-inflammatory, Fever, Head ache, Genral body pain	[5, 27, 33]
<i>Solanum nigrum</i>	Solanaceae	Kambae	Fruit	Anticancer	[35]
<i>Trigonella foenum-graecum</i>	Fabaceae	Meth	Seed	Analgesic (Back pain)	[5, 27,36]
<i>Taraxacum officinale</i>	Asteraceae	Hand	Roots	Anti-inflammatory Analgesic (Back pain)	[5, 16, 18, 27]
<i>Urtica dioica</i>	Urticaceae	Soi	Whole plant	Anti-inflammatory and Analgesic	[16, 37, 38]
<i>Viburnam grandiflorum wall</i>	Adoxaceae	Kulmunh	Barriers	Analgesic, Anticancer (Lung, breast, colon and pancreatic)	[13]
<i>Viscum album L</i>	Santalaceae	Ahul	Shoot	Hypertension & Anticancer (Lung, and pancreatic)	[5, 13, 38, 39]

5. Conclusion

In this review some anti-cancer plants have been presented which possess good antioxidant, anti-inflammatory & immunomodulatory properties leading to anticancer activity. Based on the native information collected in the study, it can be predicted that the area is a valuable source of medicinal flora with different medicinal properties. The goals for the future will be the identification, isolation, and characterization of specific molecules responsible for the bioactivity and their inherent mechanism of action and to detect and identify all stages of disease progression, prevent cancer from developing, while curing pre-existing cancers.

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