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Review Article

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ANTI-SKIN CANCER PROPERTIES OF PLANT & MARINE ORGANISM

Meenakshi Panchal*

Ass. Professor, Bhopal, M.P., India.

***Corresponding Author: Meenakshi Panchal**

Ass. Professor, Bhopal, M.P., India.

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ABSTRACT

Natural plant products consist of varieties of phyto compounds having therapeutic potential to eliminate various lethal conditions. According to the recent statistics, cases for skin cancer are increasing at an alarming rate. It also has been found to be associated with various toxic side effects and so, lack patient compliance. Therefore, there has been a need to find alternative therapeutic options with lesser side effects, to cure this deadly disease. People have been screening various plant based products with a possibility that, a thorough research on the natural plant products might lead to discovery of new chemical entities as anti-cancerous agents. Cancer chemoprevention with natural phytochemical compounds is an emerging strategy to prevent, impede, delay, or cure cancer. This review summarizes the latest research in cancer chemoprevention and treatment using the bioactive components from natural plants. Cancer chemoprevention with natural phytochemial compounds is an emerging strategy to prevent, impede, delay, or cure cancer. This review summarizes the latest research in cancer chemoprevention and treatment using the bioactive components from natural plants.

KEYWORDS: phyto compounds, skin cancer, chemoprevention, plant screening.

1. INTRODUCTION

Natural plants have been used to thwart and to treat various diseases for thousands of years.[1] Cancer is a general term applied to abnormal growth of cells that starts to grow and propagate through uncontrolled cell division and gradually expand throughout body and finally lead to death by invading and destroying normal cells.[2] Skin, the largest organ of human body, contains three kinds of cells, squamous cells, basal cells and melanocytes. Skin cancer develops in the epidermis and commonly of three types, basal cell carcinoma, squamous cell carcinoma, and melanoma[3] Cancer starts with the deformation of a natural cell caused by genetic mutations in DNA. This abnormal cell reproduces in an abnormal way by asexual reproduction, that is, it ignores signals related to regulation of cell's growth around it and obtains invasion characteristics and causes changes in surrounded tissues.[4]

What Causes Cancer?

Cancer begins with mutations in DNA, which instructs the cells how to grow and divide. Normal cells have the ability to repair most of the mutations in their DNA, but the mutation which is not repaired and causing the cells to grow becomes cancerous.[5]

Ecological Factors

Environmental factors which, from a scientist's standpoint, include smoking, diet, and infectious diseases as well as chemicals and radiation in our homes and workplace along with trace levels of pollutants in food, drinking water and in air. Other factors which are more likely to affect are tobacco use, unhealthy diet, not enough physical activity, however the degree of risk from pollutants depends on the concentration, intensity and exposure. The cancer risk becomes highly increased where workers are exposed to ionizing radiation, carcinomas chemicals, certain metals and some other specific substances even exposed at low levels. Passive tobacco smoke manifold increase the risk in a large population who do not smoke but exposed to exhaled smoke of smokers.[6,7]

Natural Sources of Anticancer Compound

An abundance of natural resources for medicinal use exist worldwide, of which many have not yet been exploited for possible application in the pharmaceutical industry. Over 50% of all available drugs on the market originated from natural sources, of which over 70% of anti-cancer agents have their origin in natural sources. Natural sources include plants, animals, microbes and marine life.[8] Plants are the most utilized natural resource for applications in the pharmaceutical science and still comprise the leading natural source for new drugs and lead compounds, due to their accessibility and abundance. To date, only a few naturally derived drugs exist on the market that target skin related cancers, whereas none have yet been approved for topical application. This could be attributed to the known side

effects of these agents when topically applied to the skin.[9]

Marine Sources

In recent years, interest in the potential of marine fauna and flora as a source of novel medicinal agents has grown significantly. Substantive research, aimed at utilizing this vast natural resource, is being carried out worldwide. The high anti-tumor potency of agents, discovered from marine resources, reflects the high potential of the ocean as a possible source of anti-cancer drugs.[10] Extracts from sponges, algae and marine cyanobacteria have shown strong anti-cancer activities. Laminarans, fucoidans, alginic acids and carrageenans are some of the compounds isolated from marine sources that have been found to exhibit effective anti-cancer activities. An assortment of polysaccharides from marine animals, bacteria and fungi have also been tested for anti-cancer activity, of which some were found promising for further drug development. Although various anti-cancer compounds from marine origin have been isolated and tested in vitro and in vivo and taken through different stages of clinical testing, only four anti-cancer drugs of marine origin have reached the market so far.[11]

Microbial Sources

The tumor regression activity of bacteria was discovered and used clinically over a century ago, when Coley observed that tumours in patients that had been accidentally infected with Streptococcus pyogenes had degenerated. Such regression was due to an immune response stimulated by the bacterial infection and it was this discovery that caused the advent of cancer immunotherapy. Ever since, much research has been performed on microbes to explore their anti-neoplastic potential. The chemical diversity and ease of access of microbes with respect to collection, culturing and fermentation make them an extremely relevant source of pharmaceutically active compounds Whole bacteria can be used in their live, attenuated, or genetically modified forms to stimulate immune responses, but this may potentially result in side effects that can be avoided by using bacterially derived products instead. Ongoing research is carried out on the use of bacterial toxins and spores and on the use of bacteria as vectors for gene therapy.[12]

Plant Sources

Over 50% of all drugs currently in clinical use worldwide have originated from compounds extracted from plants. From 1960 to 1982, the National Cancer Institute (NCI) in the USA embarked on a plant collection program, aimed at boosting progress in the discovery of plant derived anti-cancer agent. During this time, a wide range of cytotoxic agents were discovered from plant extracts, but very few of these managed to reach the market for clinical use. The development of taxanes and camptothecins as drugs for clinical use took over twenty years.[13]

Anti-Cancer Dietary Components and Phytochemicals

Phytochemicals having anti-inflammatory, immuno-modulatory and anti-oxidant properties, generally have the highest potential of exhibiting chemo-preventive behavior in skin cancers. Numerous attempts have been made to find the correlation between antioxidant properties of phytochemicals and their anti-cancer potential. Although no concrete evidence of such a correlation has been found yet, the anti-oxidant activity of a phytochemical is being regarded as an indication of potential anti-cancer activity. Carotenoids, flavonoids and terpenoids are some of the groups of phytochemicals with high anti-cancer potential.

Plant proved effect as anticancer agent

S.no.	Plant Name	Phytochemical	Part use	Skin cancer cell line	Mechanism
1)	Zingiber officinale	Gingerol (phenolic ketone)	Rhizome	Human epidermoid carcinoma cells A431	Mitochondrial membrane depolarization i.e. loss in membrane potential, increase Bax/Bcl-2 ratio, release of cytochrome c into cytosol, activation of caspase-3, -9.[14]
2)	Withania somnifera (solanaceae)	Thymoquinone	Seeds	Skin cancer	Activation of pro-apoptotic signaling via the activation of Bax, caspase-3 and cytochrome c.[15]
3)	Malus domestica (Rosaceae), kiwi, strawberry	Fisetin (flavonol)	Fruit	Mel 928 and 451Lu human melanoma cells	Downregulate frizzled, LRP6 and upregulate Axin tranmembrane receptors, dephosphorylation of GSK3β, inhibit the expression of Akt by inhibiting the phosphorylation of Ser473 and Thr308, upregulate the expression of b-TrCP expression. Inhibit the proliferation of melanoma cells by Wnt/ β-catenin pathway, reduce the level of β-catenin and Mitf[16]
4)	Silybum marianum (Asteraceae) Milk thistle	Silymarin	Seeds	Human malignant melanoma A375-S2 cells	Increase the expression of cell surface ligand death receptors i.e. Fas and Fas associated death domain (FADD) and help in activation and cleavage of pro-caspase-8 that cause cell death by apoptosis[17]

5)	Solanum panduriforme (Solanaceae)	Solasonine (steroidal	Whole plant	Melanoma UACC-62 – [100] Solanum	Cell cycle G-phase and S-phase arrest in A-375 and Hs-294T melanoma cells respectively, inhibit the protein expression of cyclinD1 and cdk-2, inhibit the protein expression of cyclinD1 and cdk-2,[18]
6)	Camellia sinensis	Epigallocatechin-3-gallate	Leaves	A-375 and Hs-294T melanoma cells	Cell cycle G-phase and S-phase arrest in A-375 and Hs-294T melanoma cells respectively, inhibit the protein expression of cyclinD1 and cdk-2, downregulate the expression of anti-apoptotic protein and increase the expression of Bax, activate the caspase -3,-7 and -9[19]
7)	Indigofera aspalathoides Vahl (Papilionaceae)	Flavone glycoside	Stem	Melanoma (LOX IMVI, MALME-3M, SKMEL-2, SK-MEL-28, SK-MEL-5, UACC-257, UACC-62) B16F-10[20]	-
8)	Rosmarinus officinalis	Ursolic acid (pentacyclic triterpenoid)	Whole plant	melanoma cells B16F-10	Upregulation of p53 protein, activation of caspase-3, downregulation of anti-apoptotic protein Bcl-2, inhibit the translocation of NF-kB to nucleus[21]
9)	Garcinia mangostana (Clusiaceae)	Xanthone (mangosteen, a-mangostin, cmangostin)	Fruit	Human melanoma SK-MEL-28, squamous cell carcinoma A-431, and skin fibroblast CCD-1064Sk cell lines	G-1 phase arrest, Upregulation of P21WAF1 expression, increase the expression of caspase-3/7, 8, membrane depolarization, increase Bax/ Bcl-2 ratio, inhibit mRNA level of Akt-1 Cell cycle G1 phase arrest, Activation of caspase-3 and decrease cell membrane potential[22]
10)	Mallotus philippinensis (Euphorbiaceae)	Rottlerin (polyphenol)	Whole	Sk-Mel-28 human melanoma cells	Downregulate the protein expression of Cyclin D1, inhibit the migration of NF-kB, inhibit protein kinase mTOR and ERK (except ERK phosphorylation)[23]
11)	Berberis aristata (Berberidaceae)	Isoquinoline alkaloids (Berberine)	Stem, rhizome and roots	Human epidermoids carcinoma cell (A431)	G1 phase arrest due to Upregulation cyclin-dependent kinase inhibitory proteins (Cip1/p21 and Kip1/p27), decrease protein expression of cyclin D1, D2 and E and also cdk2, cdk4 and cdk6, decrease the level of antiapoptotic protein Bcl-2 and Bcl-xl, increase the expression of Bax (proapoptotic protein), decrease membrane potential and activation of caspase-3, 9[24]
12)	Nigella sativa (Ranunculaceae)	Thymoquinone	Seeds	Skin cancer[25]	–
13)	Vitis vinifera (Vitaceae)	Resveratrol	Fruit	Melanoma (A-375, A-431, SK-MEL28)	Enhanced the phosphorylation of ERK1/2 without effecting the total level of ERK1/2 (A-375 and SK-MEL28 Arresting the cell at G1-phase (A431), Induction of WAF1/p21, downregulating the protein expression of Cyclin D1, D2 and E and also cdk2, cdk4 and cdk6. Upregulation the protein expression of Cyclin A, E and B1 and arresting the cell cycle at S-phase[26]
14)	Centratherum anthelminticum (Asteraceae)	Vernodaline (sesquiterpene lactone)	Seeds	Melanoma A375 cells	Enhance membrane permeability, activate caspase-9, 3, Decrease expression of Bcl-2 proteins, upregulate the expression of P53, Inhibit NF-kB pathway[27]
15)	Prismatomeris tetrandra (Rubiaceae)	Prismatomerin	Leaves and bark	SK-MEL2, SK-MEL5,SK-MEL28, UACC-62, UACC-257, M14 and MALME-3M	Antimitotic properties (inhibit spindle formation but have no effect on microtubules)[28]
16)	Betula alba	Betulin and acetylenic	Bark	Melanoma SK-MEL	Effect on human melanocortin (MC) receptor

	(Betulaceae)	derivative 28-Opropynoylbetulin		28, SK-MEL2, G361	signelling pathway, inhibit melanocyte stimulating hormone and downregulate MC1 receptor responsible for differentian and proliferation of epidermal melanocytes, Loss mitochondrial membrane integrity, activation of Caspase-3[29]
17)	Cucumis sativus (Cucurbitaceae)	Cucurbitacins (cucs) and derivatives (cucurbitacin D and J)	Fruit	Melanoma SK-MEL28[30]	-
18)	Euphorbia lagascae (Euphorbiaceae)	Polyphenol (pieceatannol)	Fruit	Melanoma SK-MEL-28	Initiate G2/M arrest by downregulating expression of cyclins A, E and B1[31]
19)	Mesua beccariana (Clusiaceae)	Non-polar extract	Stem	Melanoma SK-MEL28	Cytotoxic[32]
20)	Laurus nobilis L (Lauraceae)	Lauroside B (megastigmane glycoside)	Leaves	Human melanoma A-375, SK-MEL-28 and WM115 cells	Downregulate the expression of inhibitory apoptotic proteins i.e. XIAP and c-FLIP thus inhibit NF-kB signaling pathway[33]
21)	Glycyrrhiza glabra (Fabaceae)	Glycyrrhizin (triterpene compound), isoangustone A	Roots	SK-MEL-28 cells	G-1 phase cell cycle arrest, decrease protein expression of cyclin D1 and E, inhibit phosphorylation of Akt and GSK-3b, activities of MKK7, MKK4, P13K, block Akt/GSK-3b and JNK1/2 signaling pathways

CONCLUSION

Medicinal plants have always been an important source and played vital role in discovering new therapeutics for human diseases. For example, research on majority of ayurvedic drugs is in the pre-clinical phase or is not being actively pursued. Future research on this topic would help to identify safe and effective anticancer drugs and will further the exploration of their mechanism of action. Ayurvedic practitioners and researchers in medical sciences can help to improve this medicine by increasing their involvement and contribution. This review article highlights the effects of these plant derived phytochemicals on the skin cancer cell lines and depicts these phytochemicals to be the potential future of skin antineoplastic therapy. These plant derived constituents have majestic anticarcinogenic potential based on these in-vitro skin cancer cell lines and preclinical animal studies. Above mentioned phytochemicals exhibited eminent reduction in various skin tumors and cancers in mice but these have not yet been evaluated in humans for the prevention or treatment of various types of skin cancers.

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