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Review Article

Review on medicinal plants to target and inhibit the epidermal growth factor receptor signaling in cancer and tissue repair therapy

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Abstract

The epidermal growth factor receptor is one of the important molecular targets in cancer therapy and tissue repair, there are numerous signaling molecules involved in several functions including cell proliferation, differentiation and metastasis and suppression of apoptosis. Various methods which have been developed to target epidermal growth factor using low molecular weight small molecules and therapeutic antibodies. Over expression and activation of epidermal growth factor in tumors and tissue repair is associated with poor prognosis of patients. Therefore, epidermal growth factor represents an important molecular target for treatment in clinical oncology. Recently, the development of novel epidermal growth factor inhibitors using drugs of natural origin is urgently required. Here, we give an overview on natural products derived from medicinal herbs, food sources and microorganisms that are able to inhibit epidermal growth factor receptor signaling.

Keywords: cancer, molecular targets, signal molecules, epidermal growth factor.

INTRODUCTION

Medicinal plants have been extensively used in pharmaceutical industries and R&D sectors showing increasing interests in these products. Since centuries, natural compounds isolated and purified from various plants, animals and microorganisms and used in medicinal traditions to treat various diseases without a solid scientific basis. Now a day, it is shown that plants that were used or still to be used and are able to provide relieve for many diseases including cancer. On the other hand, use of plant extracts for treatment of burns and wound is a common practice followed over the decades and it is an important aspect of health management. So, most of the medicinal plants have a long history of curative properties in wound healing.

Epidermal growth factor

Epidermal growth factor, polypeptide hormone has been isolated from human urine (6045-Da protein with 53 amino acid residues and three intramolecular disulfide bonds) and first epidermal growth factor low molecular weight protein isolated from adult male mouse submaxillary glands[1]. Epidermal growth factor stimulates the growth of skin and corneal epithelium, potent mitogen for certain human and mouse fibroblasts in culture[2] and it is found in macrophages, human platelets, urine, saliva, milk, and plasma[3]. Epidermal growth factor (**Fig.1**) has been shown to interact with epidermal growth factor receptor on the cell surface and induced the activity of intrinsic protein-tyrosine kinase and this protein induced a signal transduction cascade that

results in a variety of biochemical changes within the cell i.e. rise in intracellular calcium levels, increased glycolysis and protein biosynthesis and also increased the expression of certain genes including the gene for epidermal growth factor receptor that ultimately lead to DNA synthesis and cell proliferation[4].

Correlation between medicinal plants with epidermal growth factor receptor and cancer

Epidermal growth factor receptors are transmembrane receptors present on the cell membranes and consists of the components of extracellular binding, transmembrane and intracellular portion of protein tyrosine kinase[5]. After ligand binding to the membrane, specific protein tyrosine residues of the intracellular domain are autophosphorylated, which results in stimulation of the intracellular signaling cascade including the Ras/Raf/MAPK (**Fig. 2**), JAK/STAT and PI3K-Akt pathways (**Fig.3**), leading to a multiple number of effects including cell proliferation and differentiation, angiogenesis, metastasis and antiapoptosis[6].

The epidermal growth factor receptor is a member of the ErbB family of receptors consists of four closely related protein tyrosine receptor kinases i.e. EGFR (ErbB1), Her2 (ErbB2), Her3 (ErbB3) and Her4 (ErbB4). These receptors activate numerous downstream pathways in response to extracellular ligands to regulate the diverse functions that include differentiation and proliferation, migration and survival. Alterations or mutations in these genes play an important role in the development and progression of many human cancers e.g. Gastric carcinomas, expression of HER1 and HER2 is thought to be a prognostic factor and target of novel biologic agents. The effect of HER3 or HER4 expression in gastric carcinomas has not been sufficiently studied. Mutations affecting epidermal growth factor receptor expression or activity could result in cancer. So, researchers focused on medicinal plants which contain chemicals that may be able to stop or inhibit the spread of cancer cells. The number of active substances which is already present in the medicinal plants may be capable of inhibiting the growth of tumor cells that are resistant to more than one drug. Thus the medicinal plants represent an excellent starting point for the development of new therapeutic treatments for cancers that do not respond to conventional chemotherapy regimens. Many plants contain toxic substances that they use to protect themselves against predators and microbial diseases. The challenge for the researchers is now to determine which plant substances are medicinal and which are simply poisonous and dangerous. Recently, most of the medicinal herbs which have been used for a long time for demanded health benefits and showed some therapeutic properties[7, 8, 9]. Therefore, now a day, researchers focus on novel drug molecules in herbs. Actually, most of the herb synthesized compounds have provided attractive possibilities for treatment strategies and also provided as dietary supplements that people take to improve their health. Medicinal herbs could serve as a promising approach for cancer treatment. Most of the medicinal herbs further insight into the molecular mechanisms underlying the clinical use of the herbs (e.g., ginsenoside and Kanglaite) as a cancer therapy. The identification of target metabolites of medicinal plant relevant to diseases allows screening for natural products capable of modulating these targets[10, 11]. This may represent the basis for the development of rational treatment of diseases such as cancer. There are number of natural products have served as structural resources in the history of drug discovery for cancer therapy.

- The effect of curcumin on antigrowth action of epidermal growth factor receptor intrinsic kinase activity in the human epidermoid carcinoma A431 cells. The cells treated for very short duration with Curcumin inhibited EGF receptor intrinsic kinase activity in a dose- and time-dependent manner and also inhibited EGF-induced tyrosine phosphorylation of epidermal growth factor receptors[12].
- One of the natural products, Korean *Panax ginseng* serves as a potential anti-cancer medicinal plant through pharmacophore-based virtual screening and molecular docking studies on epidermal growth factor receptor tyrosine kinase domain[13].
- Small cyclic peptides especially octapeptide was purified through HPLC from somatic seedlings of *Santalum album* L. (sandalwood) exhibiting potent biological activity and have great potential for anticancer therapy against human breast cancer (MDA-MB-231) cell lines[14].
- Eupatorin, constituent of *Orthosiphon stamineus*, medicinal herb giving antiproliferative activities, arrest in the G2/M phase of the cell cycle etc emerges as a promising agent in anticancer research and its leaves are used in the treatment of various disorders. The ability of eupatorin to nonspecifically inhibit many protein kinases was proven and is the probable cause of its cellular effects[15].
- The anti-cancer activity of *Pharbitis nil* (PN) ethanol extract inhibited the proliferation of MCF-7 HER2 cells. This growth inhibition was accompanied with the increase of sub G0/G1 apoptotic fractions which has been used for herbal medicinal treatment against diseases in East Asia[16].

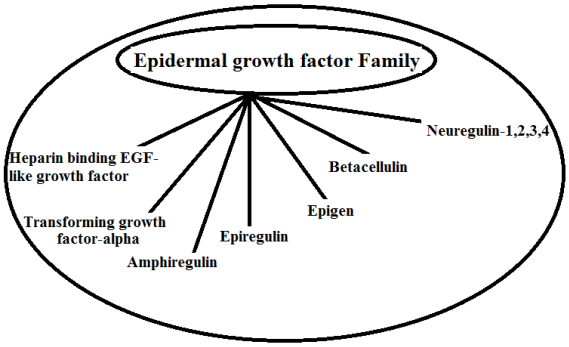
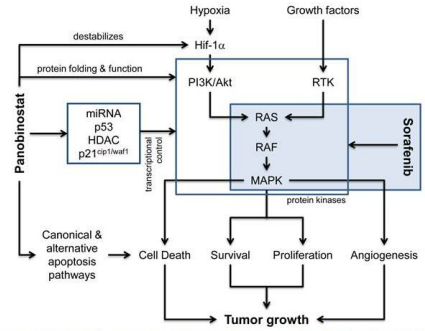
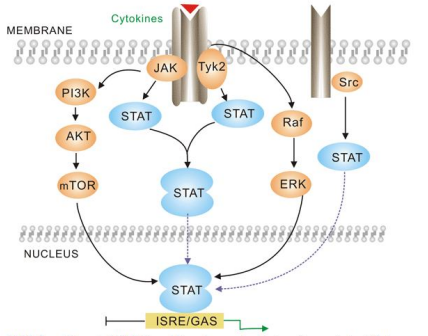


Fig.1. Family of epidermal growth factor



P13K/AKT (Phosphatidylinositide 3-Kinases); RTK (Receptor tyrosine kinase); RAS (Abbreviation of rat sarcoma); MAPK (Mitogen activated protein Kinase); miRNA (Micro RNA); HDAC (Histone deacetylase); Hif (Hypoxia inducible factor)

Fig.2. Ras/Raf/MAPK pathway



JAK (Janus Kinase); STAT (Signal Transducer and activator of transcription); Tyk (Tryosine Kinase); PI3K (Phosphatidylinositide 3-Kinases); AKT (also known as Protein Kinase B); mTOR (Mammalian target of rapamycin); ERK (Extracellular signal regulated Kinases); Src (Proto-oncogene tyrosine-protein kinase)

Fig.3. JAK/STAT and PI3K-Akt pathway

Therefore, the exact mechanisms underlying the effects of medicinal plants should be investigated further in the future to collect the information for the sustainable effect of increasing cancer specificity and reducing adverse side effects on normal tissues.

Correlation between medicinal plants with epidermal growth factor receptor and tissue repair

Tissue repair concerns many events both contractile and chemical and the causing of a wound on anybody surface stimulates the wound healing in the skin, which is a complex process characterized by angiogenesis reepithelialization, granulation tissue formation and remodeling of extracellular matrix. There are number of host defense mechanisms which are rapidly evolved to recognize viral or bacterial or fungal pathogens which render them harmless and ultimately repair the damaged tissue. This type of complex and highly regulated sequence of events can also be triggered by environmental stimuli such as noxious mechanical and chemical agents. Due to epidermal growth factor receptor becomes rapidly over-expressed following tissue injury which is followed by a progressive decline paralleling the re-epithelialization process[17]. The epidermal growth receptor is detected in fibroblasts, keratinocytes and endothelial cells which indicated the establishment of autocrine and paracrine loops by the wound's cells. It has been observed that the healing due to shrinkage observed in aged animals and humans may be related to a sensitive loss of the epidermal growth factor receptor expression especially fibroblasts[18]. The main aim of wound care is to promote wound healing in the shortest time possible with minimal pain, discomfort and scarring to the patient and must occur in a physiological environment, conducive to tissue repair and regeneration. It involves continuous cell-cell interaction and cell-matrix interactions that allow the process to proceed in different overlapping phases and processes including inflammation, wound contraction, reepithelialization, tissue remodelling, and formation of granulation tissue with angiogenesis.

India has a rich tradition of medicinal plants and these plant extracts are used by tribals who are generally used for the treatment of cuts, wounds, and burns. Most of the pharmacological reports are available on Indian medicinal plants employing various wound healing models due to disruption of the cellular and anatomic continuity of a tissue and showed its molecular mechanism[19]. Generally, wound healing consists of integrated cellular and biochemical events leading to reestablishment of structural and functional integrity with regain of strength in injured tissues[20]. There are number of natural products have served as structural resources in the history of drug discovery which correlate with epidermal growth factor for tissue repair therapy. One of the example plant polyphenols showed antioxidant and superoxide scavenging properties and these properties depends on the chemical structure of polyphenolic core and the presence of sugar moieties, time-dependently up and down regulated proinflammatory and repair regulating chemokines and accelerated *in vitro* and *in vivo* wound healing

through their interaction with different cytoplasmic and nuclear components of epidermal growth factor receptor system[21].

CONCLUSION

There is an increasing interest in finding extracts/fractions/pure molecules isolated from medicinal plants with cancer and tissue repair (wound healing efficacy) although the use of such medicinal plants for treating cancer and tissue repair is a common practice in traditional medicine.

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