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A REVIEW ARTICLE ON ALOPATHY ANTICANCER DRUG

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INTRODUCTION

Definition

"A term for diseases in which abnormal cells divide withoutcontrol and can invade nearby tissues. Cancer cells can also spread to otherparts of the body through the blood and lymph systems. There are several maintypes of cancer. Carcinoma is a cancer that begins in the skin or in tissuesthat line or cover internal organs. Sarcoma is a cancer that begins in bone,cartilage, fat, muscle, blood vessels, or other connective or supportivetissue. Leukemia is a cancer that starts in blood-forming tissue, such as thebone marrow, and causes large numbers of abnormal blood cells to be producedand enter the blood. Lymphoma and multiple myeloma are cancers that begin inthe cells of the immune system. Central nervous system cancers are cancers thatbegin in the tissues of the brain and spinal cord. Also called malignancy".

The anticancer drugs either kill cancer cells or modify their growth. However, selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy.

At present, in the modern oncology the damage of the genetic apparatus of the cell is considered to be the primary cause of cancer, and the pathogenesis of cancer is seen as a process of transformation of a normal cell into a tumor cell, as evidenced by deep fundamental research of the pathogenesis of cancer, which is held exclusively at the cellular, molecular and genetic levels of the organism.[1] Such a vector of the scientific research based on the concept of cancer as a "genes damage disease" limits the search for effective methods of cancertreatment.[2] The data on the survival of cancer patients against treatment, which for the past 30 years has only increased by 14% (from 50% to 64%).[3] can be considered as the confirmation of the insufficient efficiency of the existing approaches to cancer therapy. In addition, the incidence of cancer globally has increased in just four years from 12.7 million in 2008 to 14.1 million new cases in 2012, when there were 8.2 million deaths. Over the next 20 years, it is expected to hit 25 million a year—a 75% increase.[4] Surprisingly, this unfavourable prognosis has been made while the annual financing of scientific research of the cancer problem in the world is increasing enormously, as well as the scholars' optimism regarding the rapid creation of effective cancer drugs.

Despite the availability of the important basic knowledge about the cancer biology, the obstacle to the creation of effective cancer treatment in humans exists. In our opinion, this obstacle is the lack of the true pathogenesis of malignant tumors.

Cancer is a leading cause of mortality, and it strikes more than one-third of the world's population and it's the cause of more than 20% of all deaths. Among the causes for cancer are tobacco, viral infection, chemicals, radiation, environmental factors, and dietary factors. Surgery, chemotherapy and radiotherapy are the main conventional cancer treatment often supplemented by other complementary and alternative therapies in China.

Plants has been used as an age-old remedy of cancer history of use in the treatment of cancer. Extensive research at Sandoz laboratories in Switzerland in the 1960s and 1970s led to the development of etoposide and teniposide as clinically effective agents which are used in the treatment of lymphomas, bronchial and testicular cancer. These plants may promote host resistance against infection by re-stabilizing body equilibrium and conditioning the body tissues.[5,6]

Cancer pathophysiology

Carcinogenesis, also called **oncogenesis** or **tumorigenesis,** is the formation of a cancer, whereby normal cells are transformed into cancer cells. The process is characterized by changes at the cellular, genetic, and epigenetic levels and abnormal cell division. Cell division is a physiological process that

occurs in almost all tissues and under a variety of circumstances. Normally the balance between proliferation and programmed cell death, in the form of apoptosis, is maintained to ensure the integrity of tissues and organs. According to the prevailing accepted theory of carcinogenesis, the somatic mutation theory, mutations in DNA and epimutations that lead to cancer disrupt these orderly processes by disrupting the programming regulating the processes, upsetting the normal balance between proliferation and cell death. This results in uncontrolled cell division and the evolution of those cells by natural selection in the body. Only certain mutations lead to cancer whereas the majority of mutations do not.

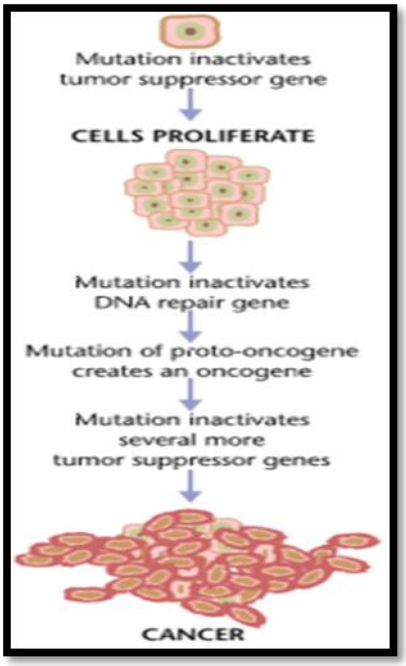


Figure:2 Genesis of cancer.

Variants of inherited genes may predispose individuals to cancer. In addition, environmental factors such as carcinogens and radiation cause mutations that may contribute to the development of cancer. Finally, random mistakes in normal DNA replication may result in cancer causing mutations. A series of several mutations to certain classes of genes is usually required before a normal cell will transform into a cancer cell. On average, for example, 15 "driver mutations" and 60 "passenger" mutations are found in colon cancers. Mutations in genes that regulate cell division, apoptosis (cell death), and DNA repair may result in uncontrolled cell proliferation and cancer.

Cancer is fundamentally a disease of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, genes that regulate cell growth and differentiation must be altered. Genetic and epigenetic changes can occur at many levels, from gain or loss of entire chromosomes, to a mutation affecting a single DNA nucleotide, or to silencing or activating a microRNA that controls expression of 100 to 500 genes.[7,8,9]

There are two broad categories of genes that are affected by these changes. Oncogenes may be normal genes that are expressed at inappropriately high levels, or altered genes that have novel properties. In either case, expression of these genes promotes the malignant phenotype of cancer cells. Tumor suppressor genes are genes that inhibit cell division, survival, or other properties of cancer cells. Tumor suppressor genes are often disabled by cancer-promoting genetic changes. Finally Oncovirinae, viruses that contain an oncogene, are categorized as oncogenic because they trigger the growth of tumorous tissues in the host. This process is also referred to as viral transformation.

Aim and objective of work

Aim of the work: A review on Allopathy anti-cancer drug

Objective of the work

- Collation of articles
- Preparation of thesis

Review of Literature

INTRODUCTION

About allopathy drug: **Allopathic medicine**, or **allopathy**, refers to science-based, modern medicine, such as the use of medications or surgery to treat or suppress symptoms or the ill effects of disease.[10]

Classification of anticancer drugs

Classification

A. Cytotoxic drugs

1. **Alkylating agents:** Mechlorethamine, Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan, Thio-TEPA, Busulfan, Carmustine, Lomustine, Dacarbazine, Temozolomide, Procarbazine
2. **Platinumcoordination complexes:** Cisplatin, Carboplatin, Oxaliplatin
3. **Antimetabolites:** Methotrexate, 6-Mercaptopurine, 6-Thioguanine, Azathioprine, Fludarabine, 5-Fluorouracil (5-FU),
4. **Microtubule damaging agents:** Vincristine (Oncovin), Vinblastine, Vinorelbine, Paclitaxel, Docetaxel, Etoposide.
5. **Topoisomerase inhibitors :** Topotecan, Irinotecan
6. **Antibiotics:** Actinomycin D, Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, Bleomycins, Mitomycin C
7. **Miscellaneous:** Hydroxyurea, L-Asparaginase, Tretinoin, Arsenic trioxide

B. Targeted drugs

1. **Tyrosine proteinkinase inhibitors** - Imatinib, Nilotinib
2. **EGF receptor inhibitors:** Gefitinib, Erlotinib, Cetuximab

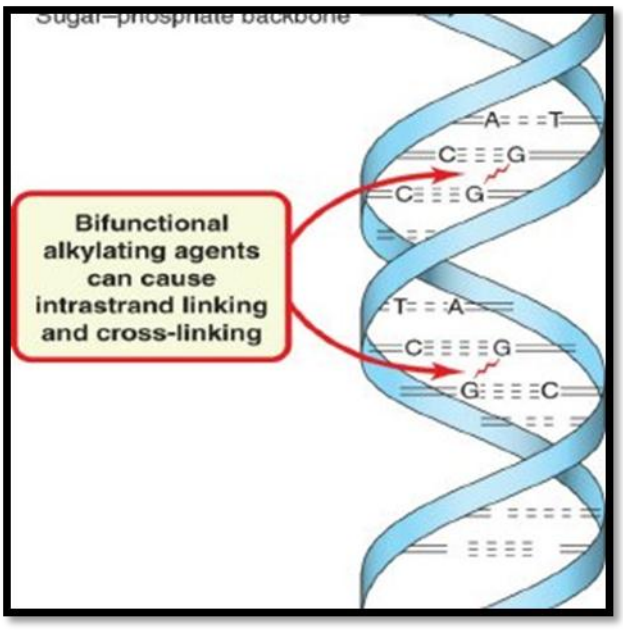
3. **Angiogenesis inhibitors:** Bevacizumab, Sunitinib
4. **Proteasome inhibitor:** Bortezomib
5. **Unarmed monoclonalantibody:** Rituximab, Trastuzumab

C. Hormonal drugs

1. **Glucocorticoids**: Prednisolone
2. **Estrogens**: Fosfestrol, Ethinylestradiol
3. **Selective estrogen receptor modulators:** Tamoxifen, Toremifene
4. **Selective estrogen receptor downregulators:** Fulvestrant
5. **Aromatase inhibitors:** Letrozole, Anastrozole, Exemestane
6. **Antiandrogen:** Flutamide, Bicalutamide
7. **5-α reductase inhibitor:** Finasteride, Dutasteride
8. **GnRH analogues:** Nafarelin, Leuprorelin, Triptorelin
9. **Progestins:** Hydroxyprogesteroneacetate, etc.

Alkylating agents[11]

The alkylating agents used in chemotherapy share the capacity to contribute alkyl groups to biologically vital macromolecules such as DNA. Modification of the basic chloroethylamine structure changes reactivity, lipophilicity, and active transport across biological membranes, sites of macromolecular attack, and mechanisms of DNA repair, all of which properties determine drug activity *in vivo.* With several of the most valuable agents (*e.g.*, cyclophosphamide and *ifosfamide*), the active alkylating moieties are generated *in vivo* after metabolism.



Mechanism of alkylating agents.

Cytotoxic actions: The most important pharmacological actions of the alkylating agents are those that disturb DNA synthesis and cell division. The capacity of these drugs to interfere with DNA integrity and function and to induce cell death in rapidly proliferating tissues provides the basis for their therapeutic and toxic properties. Whereas certain alkylating agents may have damaging effects on tissues with normally low mitotic indices for example, liver, kidney, and mature lymphocytes these tissues usually are affected in a delayed time frame. Acute effects are manifest primarily against rapidly proliferating tissues. Lethality of DNA alkylation depends on the recognition of the adduct, the creation of DNA strand breaks by repair enzymes, and an intact apoptotic response.

In non dividing cells, DNA damage activates a checkpoint that depends on the presence of a normal p53 gene. Cells thus blocked in the G_1/S interface either repair DNA alkylation or undergo apoptosis. Malignant cells with mutant or absent p53 fail to suspend cell-cycle progression, do not undergo apoptosis and exhibit resistance to these drugs.

While DNA is the ultimate target of all alkylating agents, a crucial distinction must be made between the bifunctional agents, in which cytotoxic effects predominate, and the monofunctional methylating agents (procarbazine, temozolomide), which have greater capacity for mutagenesis and carcinogenesis. This suggests that the cross-linking of DNA strands represents a much greater threat to cellular survival than do other effects, such as single-base alkylation and the resulting depurination and chain scission. On the other hand, the more frequent methylation may be bypassed by DNA polymerases, leading to mispairing reactions that permanently modify DNA sequence. These new sequences are transmitted to subsequent generations, and may result in mutagenesis or carcinogenesis.

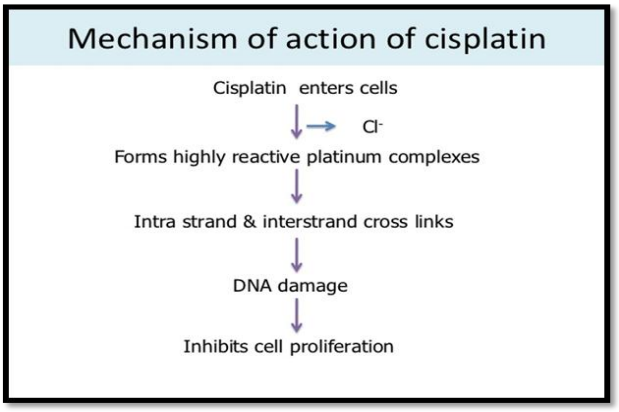
The DNA repair systems play an important role in removing adducts, and thereby determine the selectivity of action against particular cell types, and acquired resistance to alkylating agents. Alkylation of a single strand of DNA (mono adducts) is repaired by the nucleotide excision repair pathway, while the less frequent cross-links require participation of nonhomologous end joining, an error-prone pathway, or the error-free homologenous recombination pathway. After drug infusion in humans, mono adducts appear rapidly and peak within 2 hours of drug exposure, while cross-links peak at 8 hours. The half-lives for repair of adducts varies among normal tissues and tumors; in peripheral blood mononuclear cells, both mono adducts and cross-links disappear with a half-life of 12 to 16 hours.

Platinum complex

The platinum coordination complexes were first identified as potential antiproliferative agents in 1965 by Rosenberg and coworkers. They observed that a current delivered between platinum electrodes produced inhibition of *E. coli* proliferation. The inhibitory effects on bacterial replication later were ascribed to the formation of inorganic platinum-containing compounds

in the presence of ammonium and chloride ions. *Cis*-diammine dichloro-platinum (II) (cisplatin) was the most active of these substances in experimental tumor systems and has proven to be of great clinical value. Since that discovery, many platinum-containing compounds have been synthesized and tested. Carboplatin was approved for treatment of ovarian cancers in 1989, and *oxaliplatin* was approved by the FDA for colon cancer in 2003. As a group, these agents have broad antineoplastic activity, and have become the foundation for treatment of testicular cancer, ovarian cancer, and cancers of the head and neck, bladder, esophagus, lung, and colon. Although cisplatin and other platinum complexes do not form carbonium ion intermediates like other alkylating agents and/or formally alkylate DNA, they covalently bind to nucleophilic sites on DNA and share many pharmacological attributes, justifying their inclusion in the alkylating agent class.

Mechanism of action. Cisplatin, carboplatin, and oxaliplatin enter cells by diffusion, and by an active Cu^{2+} transporter. Inside the cell, the chloride atoms of cisplatin may be displaced and the compound may be inactivated directly by reaction with nucleophiles such as thiols. Chloride is replaced by water, yielding a positively charged molecule. In the primary cytotoxic reaction, the aquated species of the drug then reacts with nucleophilic sites on DNA and proteins. Aquation is favored at the low concentrations of chloride inside the cell and in the urine. High concentrations of chloride stabilize the drug, explaining the effectiveness of chloride diuresis in preventing nephrotoxicity. Hydrolysis of carboplatin removes the bidentate cyclobutane dicarboxylato group.



The platinum complexes can react with DNA, forming both intrastrand interstrand cross-links. The $N^{[7]}$ of guanine is a particularly reactive site, leading to platinum cross-links between adjacent guanines on the same DNA strand; guanine-adenine cross-links also readily form and may be critical tocytotoxicity. The formation of interstrand cross-links is less favored. DNA adducts formed by cisplatin inhibit DNA replication and transcription and lead to breaks and miscoding, and if recognized by p53 and other checkpoint proteins, induction of apoptosis. Although no conclusive association between platinum-DNA adduct formation and efficacy has been documented, the ability of patients to form and sustain platinum adducts appears to be an important predictor of clinical response.

Antimetabolites[12]

Folic acid analogs

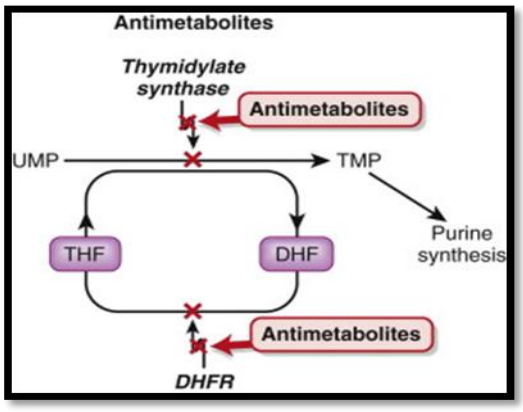
This folic acid analogue is one of the oldest and highly efficacious antineoplastic drugs which acts by inhibiting dihydrofolate reductase-blocking the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA). Utilizing the folate carrier it enters into cells and is transformed to more active polyglutamate form by the enzyme folypolyglutamate synthase (FPGS). Tetrahydrofolic acid is an essential coenzyme required for one carbon transfer reactions in *de novo* purine synthesis and amino acid interconversions. The inhibition is pseudo irreversible because Mtx has 50,000 times higher affinity for the enzyme than the normal substrate. Methotrexate has cell cycle specific action—kills cells in S phase; In addition to DHFRase it inhibits thymidylate synthase as well so that DNA synthesis is primarily affected. However, synthesis of RNA and protein also suffers.

Purine antagonists

Mercaptopurine (6-MP) and thioguanine(6-TG) are highly effective antineoplastic they inhibit the conversion of inosine mono phosphate to adenine and guanine nucleotides that are the building blocks for RNA and DNA. There is also feedback inhibition of *de novo* purine synthesis. They also get incorporated into RNA and DNA which are dysfunctional.

Pyrimidine antagonists

Pyrimidine analogues have varied applications as antineoplastic, antifungal and antipsoriatic agents.



Mechanism of action of antimetabolites.

Toxicity of anti-cancer drugs[13]

1. Bone marrow*:* Depression of bone marrow results in granulocytopenia, agranulocytosis, thrombocytopenia, aplastic anaemia. This is the most serious toxicity; often limits the dose that can be employed. Infections and bleeding are the usual complications.

2. Lymphoreticular tissue: Lymphocytopenia and inhibition of lymphocyte function results in suppression of cell mediated as well as humoral immunity. Because of action (1) and (2) + damage to epithelial surfaces, the host defence mechanisms (specific as well as nonspecific) are broken down→ susceptibility to all infections is increased. Of particular importance are the opportunistic infections due to low pathogenicity organisms. Infections by fungi (*Candida* and others causing deep mycosis), viruses (*Herpes zoster*, cytomegalo virus), *Pneumocystis jiroveci* (a fungus) and *Toxoplasma* are seen primarily in patients treated with anticancer drugs.

3. Oral cavity: The oral mucosa is particularly susceptible to cytotoxic drugs because of high Epithelial cell turnover. Many chemotherapeutic drugs, particularly fluorouracil, methotrexate, daunorubicin, doxorubicin produce stomatitis as an early manifestation of toxicity. The gums and oral mucosa are regularly subjected to minor trauma, and breaches are common during chewing. Oral microflora is large and can be the source of infection. Neutropenia and depression of immunity caused by the drug indirectly increase the chances of oral infections. Thrombocytopenia may cause bleeding gums. Xerostomia due to thedrug may cause rapid progression of dental caries.

4. GIT: Diarrhoea, shedding of mucosa, haemorrhages occurs due to decrease in the rate of renewal of the gastrointestinal mucous lining. Drugs that prominently cause mucositis are—bleomycin, actinomycin D, daunorubicin, doxorubicin, fluorouracil and methotrexate. Nausea and vomiting are prominent with many cytotoxic drugs. This is due to direct stimulation of CTZ by the drug, as well as generation of emetic impulses/mediators from the upper g.i.t. and other areas.

5. Skin: Alopecia occurs due to damage to the cells in hair follicles. Dermatitis is another complication.

6. *Gonads* Inhibition of gonadal cells causes oligozoospermia and impotence in males; inhibition of ovulation and amenorrhoea are common in females. Damage to the germinal cells may result in mutagenesis.

7. *Foetus* Practically all cytotoxic drugs given to pregnant women profoundly damage the developing foetus →abortion, foetal death, teratogenesis.

8. *Carcinogenicity* Secondary cancers, especially leukaemias, lymphomas and histocytictumours appear with greater frequency many years after the use of cytotoxic drugs. This may be due to depression of cell mediated and humoral *blocking factors* against neoplasia.

9. Hyperuricaemia: This is secondary to massive cell destruction (uric acid is a productof purine metabolism) and is especially likely to occur in leukaemias and bulky lymphomas. Acuterenal failure, gout and urate stones in the urinary tract may develop. Allopurinol is protective by decreasing uric acid synthesis. In addition to these general toxicities, individual drugs may produce specific adverse effects, e.g. neuropathy by vincristine, cardiomyopathyby doxorubicin, cystitis and alopecia by cyclophosphamide.[13]

DISCUSSION AND CONCLUSION

Chemotherapy is routinely used for cancer treatment. Since cancer cells lose many of the regulatory functions present in normal cells, they continue to divide when normal cells do not. This feature makes cancer cells susceptible to chemotherapeutic drugs. Approximately five decades of systemic drug discovery and development have resulted in the establishment of a large collection of useful chemotherapeutic agents. However, chemotherapeutic treatments are not devoid of their own intrinsic problems. Various kinds of toxicities may occur as a result of chemotherapeutic treatments. For example, 5-fluorouracil, a common chemotherapeutic agent, is known to cause myelotoxicity,[14] cardiotoxicity[15] and has even been shown to act as a vasospastic agent in rare but documented cases16. Another widely used chemodrug, doxorubicin causes cardiac toxicity,[17,18] renal toxicity[19] and myelotoxicity. Similarly, bleomycin a well known chemotherapeutic agent, is known for its pulmonary toxicity.[20,21] In addition, bleomycin shows cutaneous toxicity.[22] Cyclophosphamide, a drug to treat many malignant conditions, has been shown to have bladder toxicity in the form of hemorrhagic cystitis, immunosuppression, alopecia and at high doses cardiotoxicity.

In this study we observed that now a days most of the people in the world are suffering with cancer due to their life style, food habit and environmental pollution. For the treatment of cancer as there is no any safe compound is available. most of the anticancer drugs posses a number of side effects so more research should be carried out to establish the lead compound with fewer side effects. As newer compound with fewer side effects is need of the hour.

REFERENCES

1. Weinberg, RA. The Biology of Cancer. Garland Science, New York, 2006; 796.
2. Bizzarri, M. and Cucina, A. Tumor and the Microenvironment: A Chance to Reframe the Paradigm of Carcinogenesis? BioMed Research International, 2014; 934038.
3. Herbst RS, Bajorin DF, Bleiberg H, Blum D, Hao D, Johnson BE. et al. Clinical Cancer Advances 2005:Major Research Advances in Cancer Treatment, Prevention, and Screening—A Report from the American Society of Clinical Oncology. Journal of Clinical Oncology, 2006; 24: 190-205.
4. Stewart BW and Wild CP. World Cancer Report IARC Nonserial Publication (WHO), 2014; 630.
5. Michael S, Eran Ben-A, and Bashar S, Greco-Arab and Islamic Herbal-Derived Anticancer Modalities:

From Tradition to Molecular Mechanisms, Evidence-Based complementary and Alternative Medicine, 2012; 13.
6. Wen T, Jinjian L, Mingqing H, Yingbo Li,Meiwan C, Guosheng W, Jian G, ZhangfengZ, Zengtao X, Yuanye D, Jiajie G, Xiuping C, and Yitao W, Anti-cancer natural products isolated from chinese medicinal herbs. Chin Med, 2011; 6: 27.
7. Croce CM "Oncogenes and cancer". The New England Journal of Medicine, 2008; 358(5): 502–11.
8. Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS, Johnson JM. "Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs". Nature, 2005; 433(7027): 769–73.
9. Balaguer F, Link A, Lozano JJ, Cuatrecasas M, Nagasaka T, Boland CR, Goel A "Epigenetic silencing of miR-137 is an early event in colorectal carcinogenesis". Cancer Research, 2010; 70(16): 6609–18.
10. Weatherall, Mark W. "Making Medicine Scientific: Empiricism, Rationality, and Quackery in mid-Victorian Britain". *Social History of Medicine*, 1996; **9**(2): 175–194.
11. Flower RJ, Rijjter JM. Rang & Dale's Pharmacology, 9th Edition. Published by Elsevier.
12. Goodman & Gilman's pharmacological basis of therapeutics. New York: McGraw-Hill, 2011.
13. Rastogi N, Chag M, Ayyagari S. Int. J. Cardiol, 1993; 42(3): 285–287.
14. Aviles A, Arevila N, Diaz Maqueo JC, Gomez T, Garcia R, Nambo MJ. Leuk. Lymphoma, 1993; 11(3–4): 275–279.
15. Leo E, Arletti R, Forni F, Cameroni R. Farmaco, 1997; 52(6–7): 385–388.
16. Kilickap S, Akgul E, Aksoy S, Aytemir K, Barista I. Europace, 2005; 7(3): 227–230.
17. Manil L, Couvreur P, Mahieu P. Pharm. Res, 1995; 12(1): 85–87.
18. Gibaud S, Andreux JP, Weingarten C, Renard M, Cou-vreur P. Eur. J. Cancer, 1994; 30(6): 820–826.
19. Adamson IY. Environ. Health Perspect, 1976; 16: 119–125.
20. Parvinen LM, Kilkku P, Makinen E, Liukko P, Gronroos M. Acta Radiol. Oncol, 1983; 22(6): 417–421.
21. Karam H, Hurbain-Kosmath I, Housset B. Toxicol. Lett, 1995; 76(2): 155–163.
22. Cohen IS, Mosher MB, O'Keefe EJ, Klaus SN, De Conti RC. Arch. Dermatol, 1973; 107(4): 553–55521. Fraiser LH, Kanekal S, Kehrer JP. Drugs, 1991; 42(5): 781–795.