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Review Article

REVIEW OF RESEARCH ON GYNECOLOGICAL CANCERS IN AYURVEDA – AN UPDATE

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ABSTRACT

In spite of advanced chemotherapy and radiotherapy the term Cancer still induces fear of death in common man. Cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths (2012). Generally in the women, the five most common sites of cancer are breast, colorectum, lung, cervix, and stomach. But, the most common types of gynaecologic malignancies are cervical cancer, ovarian cancer, and endometrial (uterus) cancer etc. On par with other cancers, Gynecological cancers also contribute to significant number of deaths. In India alone, among the gynaecological cancers, breast cancer accounts for 21.5% deaths; cervical cancer for 20.7% deaths, ovarian cancer for 6.0% of deaths (World Health Organization - Cancer Country Profiles, 2014).

The main goals of a cancer diagnosis and treatment programme are to cure or considerably prolong the life of patients and to ensure the best possible quality of life to cancer survivors. Ayurveda plays a key role in prevention; prolong the life span and improvement of quality of life in cancer. In the direction of prevention of cervical carcinoma, poly-herbal compounds '*Praneem*' and '*Basant*' are studied extensively. To improve the quality of life, CCRAS have been initiated trials with coded drug AYUSH-QOL-2C, in non-metastatic breast cancer patients those who are receiving chemotherapy/radio-therapy, at St. Johns medical college, Bangalore, Karnataka. Some other clinical studies are also carried out to see the effect of turmeric as an adjuvant in abroad. Apart from the clinical trials number of single herbal drugs like *Haridra, Bhallataka, Ashvagandha* etc., and compound herbo-mineral preparations are studied to see their efficacy on different types of gynaecological cancers. In united states of America, clinical trials on arsenic preparations are also carried out. Present article aims to review the usefulness of these drugs in Gynecological cancers and their safety too.

INTRODUCTION

Cancer is a malignant growth or tumour resulting from an uncontrolled division of cells. Cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths (W.H.O). Gynecological cancers are among the most common cancers in women and became an important public health issue. Top five cancers seen in Indian women are breast cancer, ovarian cancer, colo-rectal cancer, ovarian cancer and lip/oral cancers. Ovarian cancer has emerged as one of the most common

malignancies affecting women in India and has shown an increase in the incidence rates over the years. Although cervical cancer is on a declining trend, it remains the second most common cancer in women after breast cancer.[1]

In India, every year 122,844 women are diagnosed with cervical cancer and 67,477 die from the same. India has a population of 432.2 million women (age 15 & older) at the risk of developing cancer. In the women aged between 15-44 years, cervical cancer is the second most common cancer in India. Therefore, prevention of cervical cancer is very vital in regard to Indian women[2].

One woman dies of cervical cancer at every eight minutes in India[3]. For every two women newly diagnosed with breast cancer, one woman dies of it in India[4,5,6]. Cervical and breast cancer in females accounts for over 50% of all cancer deaths in India[7]. Breast cancer is the most common cancer in women in India and accounts for 27% of all cancers in women[8]. The incidence rates in India begin to rise in the early thirties and peak at ages of 50-64 years[9]. Cervical cancer is the third largest cause of cancer mortality in India accounting for nearly 10% of all cancer related deaths in the country[10].

Economic burden of cancer: Cancer has deep economic and social impact on the people who are suffering from cancer. Often Cancer treatment pushes the families to below poverty line and threatens social security. The International Agency for Research on Cancer GLOBOCAN project[11] has predicted that India's cancer burden will nearly double in the next 20 years, from slightly over a million new cases in 2012 to more than 1·7 million by 2035. This upward trend of Gynecological cancers may be partially due to emergence of India as a fast growing economy with changes in lifestyle-related behaviour over the past twenty years.

In Ayurvedic science also there is description about the cancer like conditions of reproductive tract. In Carakasamhita and Sushruta samhita these are described under the *Yonivyapad, Artavavyapat, Raktapradara, Arbuda* etc. Based on the descriptions of symptoms and signs of the disease condition, the following conditions can be compared with Gynecological cancers - *Kunapa-granthi artavadushti, Granthibhuta artavadushti, Sannipataja pradara, Rakta arbuda, Mamsa arbuda* etc*. Kunapagandhi artava dushti* manifests with heavy bleeding per vagina with the smell of a dead body. This description indicates the early stages of endometrial carcinoma, and this condition described as incurable[12].

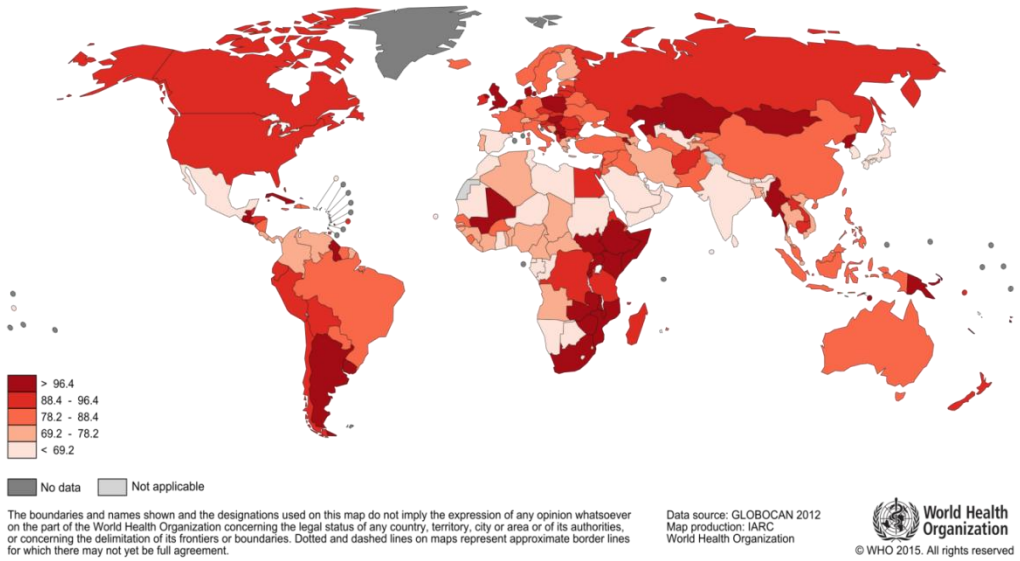
In *Granthibhuta artavadushti*, menstrual bleeding is appears like *Granthi* (clotted appearance); this condition is also described as incurable. Based on the presenting clinical features this can be compared with early stages of endometrial carcinoma[13]. *Mutrapurisha-gandhi artavadushti* presents as bleeding per vagina having smell of urine and faeces; is incurable. This condition is possible when menstrual blood is mixed with urine and faeces. This usually happens when there is formation of vesico vaginal or rectovaginal fistulas are formed. These fistula are formed in the advanced stages of malignancies of vagina, cervix etc. This condition is described as incurable[14].

There is another clinical condition described by Sushruta under *Asrugdara* called *Sannipataja asrugdara*, clinically presents with excessive bleeding per vagina having the characteristics of vitiation of all three humours, menstrual blood resembles like *Kanji* (sour gruel) in colour and has foul smell. Vagbhata described that in this condition blood colour appears blue like bronze, dirty and has foul smell. Putrid or foul smell and bleeding in different colours are the features of cervical or endometrial cancers[15].

In Ayurveda all benign tumours are described under the heading *Arbuda* and some varieties of these tumours are described as incurable like *Raktarbua*, *Mamsarbuda. Raktarbuda* is a fast growing tumour, presents with vitiated bloody discharge. *Mamsarbuda* presents a painless, stony hard, smooth, fixed swelling, which never suppurates. Both these *Arbuda* are labelled as incurable. Based on the clinical features, both of these tumours can be considered as Malignancies[16].

The main goals of cancer diagnosis and treatment programme are to cure or considerably prolong the life of patients and to ensure the best possible quality of life to cancer survivors. Prevention is really the best thing with respect to cancer; in this regard Ayurveda can play a major role. Prolonging the life span and improvement of quality of life is the second goal of treatment. In addition to this Ayurvedic drugs can also helps in reducing the side effects of chemo/radio therapy and enhance the efficacy of same drugs.

Aim of the article: Main aim of this article is to review the effectiveness of the Ayurvedic herbal and herbo-mineral preparations in the prevention, management of gynaecological cancers.



Estimated worldwide cancer mortality in women (Courtesy WHO 2015)

Prevention of Cancers

Carcinoma cervix is a major problem causing death of 510,000 women every year worldwide. A virus HPV (Human papilloma virus specially strains 16 and 18) infection of cervix initiates the transformation of cervical cells from normal to malignant cells. This transformation is a slow process and goes through various stages known as cervical intraepithelial neoplasia with stages CIN-1 CIN-2 and CIN-3. This transformation can be reversed to normal stage.

A clinical trial was carried out with the aim of elimination of HPV-16 in women with early Cervical Intraepithelial Lesions. Trial taken with a polyherbal cream called 'Basant'; containing 95% pure diferuloyl methane (E,E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), (Curcumin) from *Curcuma longa,* purified extracts of *Emblica officinalis, Neem (Azadirachta indica)* leaves, and *Aloe vera (Aloe barbadensis).* This drug was administered for 30 days as intra-vaginal tablets. Women enrolled were in reproductive age group (25 - 45 years), employing contraceptives, had regular monthly menses every 21 - 35 days, or amenorrhea due to hormonal contraceptive use, and were agreeable to abstain from non-steroidal anti-inflammatory drugs (NSAIDS) during the study period.

Women having suspicious lesions, and having persistent vaginal discharge were also included. Women who have undergone total hysterectomy, or are using intrauterine contraceptive device (IUCD) as a form of birth control method and who are pregnant or lactating were excluded from the study. Patients enrolled for this study were assigned alternatively to receive either intravaginal capsules of BASANT, two capsules (250 mg each) each night or two Placebo capsules for 30 days, excluding the days of menstrual period and they were evaluated for the presence or absence of HPV16 in cervical cells by generic and type specific PCR.

HPV DNA presence or absence was tested as primary outcome. Pap smear, visual inspection and colposcopic examination of the cervix were carried out before and after the treatment, to study the effect of treatment on the lesion and on cytology as outcome. Out of 35 subjects enrolled, 19 patients were found positive for HPV-16. Only 11 out of these 19 agreed to undergo intravaginal treatment with BASANT. After 30 days of intravaginal insertion of BASANT, all eleven HPV-16 positive cases became HPV negative.[17, 18]

Another study carried out by team of scientists from Division of Molecular Oncology; Division of Cytopathology, Division of Clinical Oncology of Institute of Cytology and Preventive Oncology (ICMR), Noida and Department of Obstetrics and Gynecology, Lok Nayak Hospital, New Delhi on Cervical Pre-cancerous lesions. They have developed a polyherbal formulation called 'Praneem', and carried out a study to evaluate the potential of anti-HPV activity of Praneem in women infected with high risk HPV type 16. Study was carried out on twenty women who were molecularly diagnosed as positive for HPV16 infection without or with low grade squamous intraepithelial lesion (LSIL) or inflammation and assigned to intra-vaginal, topical application of either Praneem tablet or placebo for 30 days excluding the days of menstrual period and were evaluated for persistence of HPV infection using

HPV L1 consensus and HPV type 16-specific PCR as primary outcome.

In 6 out of 10 (60%) women, after one course of Praneem treatment, HPV was eliminated. A repeated treatment in remaining four patients with persisting HPV infection, resulted in clearance of HPV in two additional cases; and this resulted in an overall 80% clearance of HPV 16 as against a spontaneous clearance of 10% (1/10) seen in the placebo arm. The elimination of HPV DNA was found to be accompanied by marked improvement in clinical symptoms and cytological abnormalities of Praneem-treated patients. Finally the result showed that a 30-day intra-vaginal application of the Praneem can result in elimination of HPV infection from the uterine cervix. A disadvantage of Praneem was the irritation that was observed in some subjects[19].

A pilot study carried out as integrative therapy on Low-grade Squamous Intra-epithelial Lesion persistent after antimicrobial treatment and treated with oral administration of a standardized extract of Turmeric Oil (coded as NBFR-03). A total of 1473 women were screened through Papsmear, among those 88 cases had Low-grade Squamous Intra-epithelial Lesion. Among these women, only those having persistent Low-grade Squamous Intra-epithelial Lesion subsequent to antimicrobial therapy, and willing to follow the protocol (N=21), were included in the study. Clinical examination, Pap smears, colposcopy, clinical biochemistry, urinalysis and assessment of serum IL-6, were carried out before and after treatment. Standardised NBFR-03 (0.2gm) capsules were administered, twice daily, for 12 weeks. Out of 21, 19 women completed the study, in none of the case pathology progressed further and 16 cases shown regression to Atypical or Negative smears[20].

Improvement of Quality of life in Cancer patients

Some research studies are carried out for improvement in quality of life in cancer patients. Central Council for Research in Ayurvedic Sciences, an apex body of research in Ayurveda developed AYUSH-QOL -2C a coded drug and taken up collaborative study in the patients those who receive chemotherapy/radio-therapy in cases of breast cancer with St. Johns medical college, Bangalore. This was a Randomized Double Blinded Placebo Controlled trial, and executed at St. Johns Medical College and Hospital to assess the efficacy and safety and to evaluate Quality of Life with Ayush QOL 2C in patients of Non Metastatic Breast Cancer as a supplement to adjuvant Chemotherapy. Dose of the trial drug two capsules twice in a day for 6 months in 80 patients diagnosed to have breast cancer and are operated for the same and are receiving chemotherapy of 4 or 8 cycles. The Primary outcome of the study was efficacy of AYUSH QOL 2C in improvement in quality of life in comparison to placebo. Secondary outcome was safety of AYUSH QOL 2C as a supplement to adjuvant chemotherapy during each cycle and at sixth month, ninth month and at the end of one year. The assessment of efficacy of patients was carried out using Visual Analogue Scale, FACT-B (Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer) and ECOG (Eastern Cooperative Oncology Group) scale as well as hematological, biochemical and clinical examination was adopted to report on severity of toxicity experienced by patients on oncology treatment trials. This trial is completed but, results not yet published[21].

Note: VAS –Visual Analogue Scale - is commonly used to rate various subjective experiences; in cancer patients it is used to analyse the quality of life; QOL scores may reflect physical or psychosocial functioning or distress.

FACT-B – Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer, Breast Cancer Chemotherapy Questionnaire developed to measure outcomes of women with stage II breast cancer receiving adjuvant chemotherapy.

ECOG: Eastern Cooperative Oncology Group (ECOG PS) - is used by physicians to report on severity of toxicity experienced by patients on oncology treatment trials. The ECOG measures toxicity effects on a five-point scale with 0 being "fully active, able to carry on all pre-disease performance without restriction" and 5 indicating that the patient is deceased.[22]

Clinical trials on Adjuvant therapy

A Study carried out to see the feasibility and tolerability of the combination of docetaxel and curcumin, a polyphenolic derivative extracted from *Curcuma longa* as an adjuvant therapy on Patients with advanced or metastatic breast cancer. Docetaxel (100 mg/m2) was administered as a 1-hour I.V. infusion every 3 weeks on d1 for 6 cycles. Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Curcumin was orally given from 500 mg/d for 7 consecutive days by cycle (from d-4 to d+2) and escalated until a dose-limiting toxicity should occur.

The primary endpoint of this study was determination of the maximal tolerated dose of the combination of dose-escalating curcumin and standard dose of docetaxel chemotherapy in advanced and metastatic breast cancer patients. Secondary objectives included are toxicity, safety, vascular endothelial growth factor and tumor markers measurements, and assessment of objective and clinical responses to the combination therapy.

Results observed was - at the last dose level of curcumin, 3 dose-limiting toxicities were observed and 2 out of 3 patients at this dose level refused to continue treatment; this led the researchers to define the maximal tolerated dose of curcumin at 8000 mg/d. The efficacy of the drug was enhanced. The recommended dose of curcumin is 6000 mg/d for 7 consecutive days every 3 weeks in combination with a standard dose of docetaxel[23].

Another study was carried out to assess the ability of the Curcumin to reduce radiation dermatitis severity in 30 breast cancer patients. Designs of the study was randomized, double-blind, placebo-controlled clinical trial. In this study adult female with non-inflammatory breast cancer or carcinoma in situ prescribed radiotherapy without concurrent chemotherapy were included. Randomized patients took 2.0 grams of curcumin (trial group) or placebo orally three times per day (i.e. 6.0 grams daily) throughout their course of radio therapy. Assessments were done every week based on Radiation Dermatitis Severity (RDS) score, presence of moist desquamation, redness measurement, McGill Pain Questionnaire-Short Form and Symptom Inventory questionnaire. The 30 evaluable patients were primarily white (90%) and had a mean age of 58.1 years.

Standard pooled variances t test carried out, it showed that curcumin reduced RDS at end of treatment compared to placebo (mean RDS = 2.6 vs. 3.4; P = 0.008). Fisher's exact test revealed that fewer curcumin-treated patients had moist desquamation (28.6% vs. 87.5%; P = 0.002). No significant differences were observed between arms for demographics, compliance, radiation skin dose, redness, pain or symptoms. In conclusion, oral curcumin, 6.0 g daily during radiotherapy, reduced the severity of radiation dermatitis in breast cancer patients.[24]

Herbal drugs

A). *Haridra* - *Curcuma longa:* So far no known pharmaceutical drug effectively prevents breast cancer metastasis. However, new research from the M.D. Anderson Cancer Center at the University of Texas in Houston suggests that consuming adequate amounts of the common spice curcumin may halt the spread of breast cancer in its tracks[25]. Curcuma also exhibited number of anticancer activities on pharmacological studies. Curcumin's inhibition of breast cancer metastasis in the new mouse study appears to rest on its ability to suppress a substance called nuclear factor kappa B (NF-?B). Other activities found are - promotion of apoptosis, potentiating the effects of other forms of chemotherapy, inhibiting angiogenesis.

In another well-controlled clinical trial, patients with various high-risk premalignant lesions took curcumin for three months at daily doses ranging from 1 g to 12 g. Improvement in the lesions was noted in one of four patients with uterine cervical intraepithelial neoplasm, a precancerous condition of the uterine cervix. Most importantly, there was absolutely no toxicity in these patients at doses up to 8 g per day. While the 12 g dose was also nontoxic, it was deemed unacceptable because the volume of curcumin was so large.[26]

B). *Bhallataka - Semicarpus anacardium*

This drug was studied extensively for its Anti-carcinogenic activity in the Department of Shalyatantra, Institute of medical sciences, Benarus Hindu University, Varanasi as an adjuvand drug. Extensive pharmacological screening of this drug also been done by many allied scientists worldwide.

Mathivadhani et al. studied *Bhallataka* nut extract for inhibitory effect on human breast cancer cells (T47D). Cytotoxicity analyses suggested that these cells had become apoptotic. *Semecarpus anacardium* was discovered to induce rapid Ca(2+) mobilization from intracellular stores of T47D cell line, and its cytotoxicity against T47D was well correlated with altered mitochondrial trans-membrane potential. At the molecular level, these changes are accompanied by decrease in Bcl(2) and increase in Bax, cytochrome c, caspases and PARP cleavage, and ultimately by internucleosomal DNA fragmentation. Results of this study provided unprecedented evidence that *Bhallataka* triggers apoptotic signals in T47D cells[27].

Another study carried out with two groups, first group with '*Kalpamruta'* (KA) containing *Semicarpus anacardium* as main ingredient; second group with plain *Semicarpus anacardium* (SA) in breast cancer induced rats. *Kalpaamruthaa* (KA) is a modified Siddha preparation, which contains *Semecarpus anacardium* Linn., *Emblica officinalis* and honey. The study carried out to assess the variations in lipids, lipid-metabolizing enzymes and

lipoproteins in cancerous animals and the effect of KA on the lipid metabolism. The effects of first group (KA) were found to be more effective than second group (SA). No significant alterations were observed in herbal preparation control animals when compared to control animals[28].

C. *Ashwagandha – Withania somnifera*

Ashwagandha considered as the king of the medicinal plants, is also studied extensively for its different pharmacological actions. A study carried out the leaf extract of this drug for its anti-proliferative activity on MCF-7 (breast) human tumor cell lines. Compounds 1-12 and diacetyl withaferin A were shown to produce anti-proliferative activity on MCF-7 (Breast) human tumor cell lines[29]. Withaferin A has been found to inhibit growth of MCF-7 and MDA-MB-231 human breast cancer cells in culture and MDA-MB-231 xenografts in vivo by causing apoptosis[30].

A novel bioactive compound withanolide sulfoxide obtained from methanol extract of *Withania Somnifera* roots has been shown to suppress human tumor cell proliferation and its IC50 value against human breast (MCF-7) cancer cell lines in the range of 0.74-3.63µm[31].

D. *Rohitaka/Rohituka - Amoora rohituka*

This plant also studied extensively in the Department of Shalyatantra, Institute of Medical Sciences, Benarus Hindu University for its ante-cancer activities. Triterpenic acid, amooranin, extracted from the bark of *Amoora rohituka* trees, has been reported to possess significant anticancer potential[32]. Amooranin has been shown to induce apoptosis in breast carcinoma through caspase activity[33].

E. *Devadaru –Cedrus deodara*

In vitro cytotoxicity studies showed significant dose-dependent effects against several cancer cell lines from different tissues such as breast, cervix, neuroblastoma, colon, liver, and prostate at 10, 30 and 100 microg/mL. The IC (50) values varied from 16.4 ng/mL to 116.03 microg/mL depending on the cell line[34].

Apart from the above, some other medicinal plants are also found effective on pharmacological studies in Gynecological cancers. Details are given below:

- *Ipomoea squamosa* - Ovarian cancer
- *Curculigo orchioides* - Breast cancer
- *Citrullus colocynthis* - Breast cancer
- *Semecarpus anacardium* - Breast adeno carcinoma, cervical epithelial carcinoma
- *Berberis vulgaris* - Breast cancer
- *Bidens pilosa* - Cervix cancer
- *Ocimum gratissimum* - Breast cancer

Mineral drug – Arsenic trioxide

Arsenic trioxide is a chemotherapy drug treatment for acute promyelocytic leukaemia (APL). Arsenic trioxide is found to inhibit growth and promotes apoptosis in many different cancer cell lines. The National Cancer Institute (US) is working cooperatively with research centers across the U.S. to evaluate its clinical activity in hematologic malignancies - such as acute promyelocytic leukemia, acute myeloid leukemia, etc., and multiple myeloma. It is also supporting research in solid tumors, such as advanced hormone-refractory prostate cancer and renal cell cancer and in cervical cancer and refractory transitional cell carcinoma. US Brand name for Arsenic trioxide is Trisenox and is approved by FDA.

A study carried out at Memorial Sloan-Kettering Cancer Center with focus on patients with advanced cervical cancer; showed that arsenic trioxide induces apoptosis in HPV 16 DNA-immortalized human cervical epithelial cells in vitro and selectively inhibits early viral gene expression[35]. Inclusion of arsenic in the media proved cytotoxic for a variety of cell lines, including those for bladder and cervical cancers[36]. Based on these trials on Arsenic oxide, Ayurveda people can also take up trials with *Bhasmas* of *Gouripashana, Manahshila* and *Haratala*, since these are the ores of arsenic.

Compound drug

Ayurvedic compound drug containing *Semecarpus anacardium, Amura rohitaka, Glycyrrhiza glabra* and copper powder were reported to inhibit breast tumour development in mice by significantly extending the survival period. This drug was also found to be efficient in clinical trials. Experimental study carried out with this drug on 100 young female mice, each 50 were allocated under trial and control groups. Trial group mice revealed a significant inhibition of the rate of development of tumour in comparison to control group; showed survival period up to 50 – 60 days in relation to the 100% mortality within 20-30 days in control group.

Clinical study also carried out under five groups Group-I with Chemo+Radio+Ayurvedic trial drugs; Group-II with Chemo+Radio therapy, Group-III with Chemotherapy+Ayurvedic trial drugs, Group-IV with Chemotherapy alone and Group-V with Ayurvedic trial drug alone. Complete response was observed in Chemo+Radio therapy+Ayurvedic trial drug group[37].

CONCLUSION

After studying pharmacological studies and clinical trials on single herbal drugs, compound herbo-mineral drugs it can be concluded that;

1. There is a hope for the development of comprehensive Ayurvedic regimen for the cure of early stage of Cancer
2. To obtain strong curative effect, pharmacological and clinical trials are need to be carried out with *Vishavarga* drugs as well as metallic *Visha* drugs like *Haritala, Manahshila, Gouripashana* etc.
3. Extensive Clinical trials are to be carried out with the pharmacologically proved herbal, herbo-mineral compound drugs.
4. Ayurvedic are also found effective in preventing the gynecological cancers through reversing cytological changes that occurring in the target organs for example – low grade cervical intraepithelial neoplasia.
5. Some drugs like *Haridra* are effective in reducing the Chemotherapy/radiotherapy induced side effects and enhancing the bioavailability of the drugs.
6. Another important aspect of Cancer management is improvement of quality of life; in this direction studies are going on, results are yet be published.

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