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EVIDENCE BASED ANALYSIS OF A POSSIBLE THERAPEUTIC ROLE OF GUM GUGGAL [*COMMIPHORA WIGHTII* (ARNOTT.) BHANDARI. (AN AYURVEDIC DRUG) IN CANCER; A PHARMACOLOGICAL APPROACH)

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ABSTRACT: Cancer is a devastating disease affecting human population and challenging its personal, social and economical facets along with giving a lot of pain and agony. It has also posed a great challenge to the medical fraternity and also the biomedical scientists in terms of curability, recurrence and drug discovery. If not treated earlier, it is obviously life threatening. Traditional medicines have not been properly explored in the treatment of cancer. Gum Guggal commonly called as Guggulu (*Commiphora wightii*) in Ayurveda is one such drug used in Ayurvedic clinical practice since time immemorial in various inflammatory clinical conditions like Sopha (inflammation), Dusta Vrana (chronic unhealed ulcer), Galaganda (Thyroiditis), Apachi (scrophula), Gandamala (cervical lymphadenitis), Arvuda (malignant tumor), Granthi (benign tumors) etc. Inflammatory pathway is known to be over-activated in cancer. Since Guggulu in Ayurveda is an anti-inflammatory and analgesic drug and is clinically used in various cancer related conditions, it is judicious to make a review on the anti-cancer potential of Gum Guggal in order to establish it as an anti-cancer drug either for monotherapy or for combined therapy in cancer. In this paper attempts have been made to compile the properties, actions and indications of Gum Guggal mentioned in Ayurvedic literature in various cancer related clinical conditions. Again, attempts are also made to compile the results of various preclinical and clinical studies conducted on Guggulu and its constituents and published in different journals and database with reference to their cytotoxic, anti-inflammatory, anti-oxidant and related immunomodulatory activities with special reference to its molecular mechanism of action. The review suggests that *Commiphora wightii* can be a potential therapeutic agent for the treatment of various types of cancer either for monotherapy or for combined drug therapy along with conventional anticancer drugs.

INTRODUCTION: Cancer is a devastating disease affecting human population and challenging their personal, social, economical aspects along with giving a lot of pain and agony. If not treated earlier, it is obviously life threatening. It has also posed a great challenge to the medical fraternity and also the biomedical scientists in terms of curability, recurrence and drug discovery. Early diagnosis and early initiation of treatment may increase the chances of curability and survival.

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Currently cytotoxic drugs, surgery, radiotherapy and immunotherapy are main stay of cancer treatment [1]. Traditional medicines like Ayurveda have not been properly explored in the treatment of cancer. Of course, it is an admissible fact that there has been a tremendous upsurge in the research and development front of traditional medical herbs for

evaluating their anti-cancer potential. The concept also applies to Ayurvedic medicinal plants [2]. Gum Guggal commonly referred to as Guggulu (*Commiphora wightii* Engl.) is one of the important medicinal plants used in Ayurveda specifically for pain and inflammatory conditions. Inflammatory pathway is over activated in cancer. Therefore, it is justified to make a review on the anti-cancer literature on Guggulu in order establish it as an anti-cancer drug.

Brief Literature Review on Cancer: Cancer is a disease of cells due to uncontrolled cell division and proliferation characterized by tumor formation, metastasis, anaplasia and invasiveness. The imbalance between cell production and cell death due to the failure of mechanism of cell destruction due to apoptosis is the main reason behind cancer. It is otherwise called malignant tumor or neoplasia and is normally appeared after 40 years of age although some kinds of cancers can also appear during child hood. Common etiological factors include exacerbated life style like tobacco, alcohol consumption, exposure to chemical carcinogens (cholanthrene, methyl cholanthrene, polycyclic hydrocarbon benzopyrene group of chemicals, chromium, nickel, vinyl chloride *etc*), occupation (exposure to asbestos, silica, arsenic, benzene *etc*), age (old age), sex (breast and cervix cancer in women), hormones (estrogen, progesterone, testosterone in cancers of breast, endometrium and prostate), viruses (Epstein Barr virus causing Burkitt's lymphoma, Hepatitis B and C virus causing hepatocellular carcinoma, human T lymphotrophic virus type-1 can cause human T-cell leukemia *etc*).

Apart from these aflatoxins, radiation in all forms, immunodeficiency states, sedentary lifestyle and some particular food habits can also cause cancer in various forms. The World Health Organisation (WHO) projects one in every ten persons in India will develop cancer in his lifetime while one in fifteen persons will die out of it. In India oral cancer dominates in males while breast cancer dominates in females. Currently surgery, cytotoxic drugs, radio therapy and immunotherapy are the main stay of cancer treatment whose success rate is self limiting in character [3]. Malignant tumors are usually large in size, rapidly growing, poorly circumscribed and apparently without any encapsulation. They are anaplastic with less or no differentiation with frequent mitosis and pleomorphism. They are always with a poorly formed stroma and are usually fixed to the surrounding tissues showing more tendencies to haemmorhage and ulceration due to increased vascularity to the tumor. Death occurs due to combination of mechanical and destructive effects together with blood loss, secondary infection, starvation, cachexia, marrow replacement by metastasis, anemia, malnutrition *etc* [4].

The malignant tumors of epithelial origin are called carcinoma and those of mesenchymal origin are called as sarcomas. In general, malignant tumor cells have increased mitotic rate and slower death rate. Another proposition is that cancer cells arise from the stem cells which are present in the tissue in a small number which have the capacity of prolonged self renewal. They are mono-clonic in origin. Various growth factors secreted by the tumor cells which are responsible for tumor formation are Epidermal growth factor (EGF), Fibro-blast growth factor (FGF), Platelet-derived growth factor (PDGF), Colony stimulating factors (CSF), IL-1, IL-6, Vascular endothelial growth factor(VEGF), Transforming growth factors(TGF-β) *etc*. Upregulation of different intercellular communication pathways like NfKb, Akt, STAT-3, β-catenin, FAK, Src kinase signaling, MUC-4 gene expression, JAK kinase mediated signaling and down regulation of ERK signaling pathway, mitochondrial apoptotic signaling pathway are also responsible for the genesis of cancer in its various forms.

Among the cell signaling enzymes and proteins, upregulation of DNA methyltransferase, Bcl-2 group of proteins, JNK kinase, Cyclin-D-1, cdc-2, IGF-1-Rβ proteins, IL-1-β, micropthalamia associated transcription factor(MATF), TRP-1, TRP-2, Phosphotyrosine, Tyrosinase enzymes, Telomerase enzyme, extra-cellular matrix and down regulation of caspase enzyme group, ERK/MAPK (serine/threonine protein kinase), JNK, P-21, P-27, poly(ADP-ribose) polymerase (PARP), Bax, Bik and Bim are also responsible for causing mutation and uncontrolled cell division. Among the inflammatory pathway pro-inflammatory cytokines, cyclo-oxygenase (COX), high-sensitive C-reactive protein (hs-CRP) etc are

over expressed. There is also a failure of cytotoxic T lymphocyte, NK cells and Phagocytes on the immunological axis. Down-regulation of antioxidant enzymes like GPO, GPX, CAT, Glutathione and over production of oxygen and nitrogenous free radicals are also involved in the formation of cancer [4].

Cancer is initiated through genetic alterations through mutations to onco-suppressor genes, proto-oncogenes and DNA repair genes. Down regulation of onco-suppressor genes(APC, BRCA-1, BRCA-2, RB-1, TP-53, WT-1 etc) and DNA repair-genes(BRCA-1, BRCA-2) and upregulation of proto-oncogenes (ABL-1, HER-2, MYC, RAS, SIS etc.) as a result of accumulated mutations which could be due to the activation of various pathways like inflammatory pathway, oxidation pathway, immunological pathway, carcinogenic pathway and various other intercellular communication pathways [4].

Literature Review on Guggulu: Guggulu or Gum guggal is one of the important medicinal plants used in various Ayurvedic medicinal preparations specifically for pain and inflammatory conditions like arthritis, gout, hypercholesterolemia, cervical lymphadenitis, goiter, tumors, cysts etc. Various Sanskrit synonyms have been attributed to Gum guggal. They are Devadhupa, Jatayu, Kaushika, Pura, Kumbha, Ullukhala, Mahisaksha, Palankasha. It is botanically identified as *Commiphora wightii* Syn *Commiphora mukul* Engl. Syn. *Balsamodendron mukul* Hook. ex Stocks. and belongs to the family burseraceae. In English it is regarded as Gum Guggal or Indian bedellium. The drug consists of the oleo-gum resin obtained by giving incision to the bark of the matured plant [5, 6].

Distribution: The global distribution of the plant is restricted to Rajasthan, Punjab, Gujrat, Mysore, Madhya Pradesh, part of Maharashtra, Karnataka in India and adjoining areas of Punjab, Rajasthan, and Gujarat in Pakisthan. It is found wild and is also cultivated. It prefers an arid or semi-arid climate for its growth. It is a plant native to Indian subcontinent [5, 6, 7, 8].

Conservation Status: *Commiphora wightii* (CW) has been overharvested because of its adequate use in Indian systems of medicines. In the two largest habitats of Guggulu, Gujrat and Rajasthan, it has become scarce due to unsustainable collection of multiple parts, high volume trade and loss of habitat. Over exploitation, a small area of occurrence, fragmented population, very low regeneration and invasion of alien species have put CW in a high extinction risk. Each mature plant gives an average of 250-500 gms of gum during the extraction season i.e from November to December. The International Union for Conservation of Nature and Natural resources (IUCN) has put the plant under IUCN red list of threatened species and is grouped under critically endangered category [7, 8, 9].

Conservation Majors: For conservation & development of Guggul in Gujarat, the National Medicinal Plant Board (NMPB) has supported projects through Department of Environment & Forest, Gujarat State Government during the financial year 2007-08 & 2010-11 with the objective to establish Medicinal Plants Conservation Development Areas (MPCDAs) for this species. Six Medicinal Plants Conservation Development Areas (MPCDAs) namely Mangvana, Gugliayna, Tharvada, Ler, Mathal & Kurboi Nabahoi in Kachchh Circle (Gujarat) have been established to cover an area of about 1200 hectares. Wild population of the CW plant is conserved which could be a source for future use of raw drug, gene bank and wild source for future research & development. In addition, various activities have been taken place for execution of Guggul project such as rising of nurseries, area development, soil moisture conservation works and fencing of area. The farmers and the forest staff are also trained regularly for the mass scale cultivation of Guggul in the Gujarat State [7, 8, 9, 10].

Morphology: CW grows as a spinous shrub or a small tree reaching a maximum height of 4 meters (13 feet) with greenish yellow thin papery bark. The branches are thorny and spreading. The leaves are simple or trifoliate. Leaflets ovate, 1-5 cm (0.39-1.97 in ch) long, 0.5 to 205 cm (0.20 to 0.98 inches) broad and irregularly dentate, glaucous and shinny. Flowers are gynodioecious with some plants bearing bisexual and male flowers and others with female flowers. The individual flowers are red to pink with four small petals. The small round fruit are red when ripe [5, 11].

Collection of the Oleogum-resin: The oleogumresin of Guggulu is collected by making a deep incision at the basal parts of the stem bark of CW. The ethyl acetate extraction separates the oleogum resin into two parts, gum and resin and further separates it into acidic, basic and neutral fraction containing appropriate fractions of guggulusterone [12].

Varieties of Guggulu: As per Ayurvedic literature five varieties of Guggulu have been described. They are Mahisaksha, Mahaneela, Kumuda, Padma, Hiranya. Mahisaksha Guggulu resembles the black color of Bhrunga (bumble bee) or Srotanjana, Mahaneela is deep blue in color, Kumuda resembles the colour of water Lily flower (Kumuda Pushpa).

Padma resembles the colour of Ruby (Manikya). Hiranyaksha Guggulu bears the color of gold. Only Mahisaksha and Hiranyaksha Guggulu have been prescribed for human consumption. Again, there is another classification available in Ayurvedic literature in terms of fresh (Navina) and old varieties (Purana). New or freshly collected Guggulu nourishes the body and promotes the tissue elements. It increases the quantity of semen.

The fresh Guggulu resembles the color of gold, unctuous and lubricating and the color is identical to the ripened Jamun fruit with good aroma. On the contrary, the old variety of Guggulu is dry, with fowl smelling, devoid of natural color and complexion and is devoid of therapeutic potency and is more than five years old. But Sushruta describes an old variety of Guggulu is extremely weight reducing and emaciating in character [5].

Purification of Guggulu: Collected dried gum resin of Guggulu is boiled over low temperature with double quantity of decoction of Triphala (equal parts of fruits of *Terminalia chebula, Embelica officinalis* and *Terminalia belerica*) or Guduchi (*Tinospora cordifolia*) or milk till Guggulu is completely dissolved in the solvent. Once it is completely dissolved, decant the liquid part leaving the residue in the container. Now concentrate the liquid part over low temperature with intermittent sprinkling of Ghee, around one sixteenth part of Guggulu [13].

Properties, Actions and Indications:

Properties: Guggulu has been attributed with Katu (pungent), Tikta (bitter), Kashaya (astringent) Rasa (Taste) in Ayurveda. It bears Laghu (light), Ruksha (dry), Tikshna (sharp), Visada (clear) and Sara (stable) properties (Guna). It is hot (Ushna) in potency (Veerya) and is Katu (pungent) in digestion (Vipaka).

These are the pharmacodynamical factors by virtue of which it exhibits its therapeutic actions as per Ayurvedic literature. It pacifies all the three Doshas, but specifically Kapha and Vata. It is one of the best among the Vatahara Dravyas. From the sweet taste, it pacifies Vayu, from astringent taste, it pacifies Pitta, from bitter taste, it pacifies Kapha and accordingly Guggulu pacifies all the three Doshas [5].

Actions: The oleoresin of Guggulu promotes the union of bones in bone fracture. It works as aphrodisiac (Vrishya), exhibits sharp actions (Sukshma), improves voice quality (Swarya), rejuvenates the tissues (Rasayana), improves digestion (Deepana), promotes physical endurance (Balya) and helps in the healing of wounds (Vrana Ropaka). It has also anti-obesity actions. Guggulu gum has also blood purifying activity [5].

Indications: Guggulu is an important drug in Ayurveda. It is indicated in various clinical conditions like Bhagna (bone fracture and dislocation), azoospermia, hoarseness of voice, malnutrition, dyspepsia, wounds and ulcers, Apachi (cervical lymphadenitis), Medoroga (obesity), Prameha (Polyurea), Ashmari (urinary calculi), Vata Vyadhi (diseases of the nervous system), Kleda (wet skin), Kustha (skin diseases), Amavata (rheumatoid arthritis), Pidaka (carbuncles), Granthi (cysts), Sopha (edema/ inflammation), Arsha (haemmorrhoides), Gandamala (cervical lymphadenitis), Krimi (helminthes). Guggulu has been considered one of the best treatments for all kinds of Avruta Vata.

The oleogum-resin of CW is indicated in chronic bronchitis, cough and diseases of the nervous system like sciatica (Grdhrasi), facial paralysis (Ardita). Apart from this Guggulu is also indicated in indigestion (Ajeerna), diarrhea (Atisara), dyssentary (Amatisara), Gandamala (cervical lymphadenitis), Granthi (cysts), abscess (Bidradhi),

skin diseases (Kustha), syphilis (Phiranga), all kinds of inflammations (Sopha), ascites (Udara), ulcers and wounds (Vrana), fistula in ano (Bhagandara), helminthiasis (Krimi), anemia (Pandu), haemmorrhoides (Arsha), polyurea (Prameha), diseases of the uterus (Yoni Vyapad), obesity (Medoroga), lumbago (Katishula) *etc* [5, 14].

Factors to be Avoided During the Guggulu Therapy: A person on Guggulu therapy should avoid sour (Amla), sharp (Tikshna), indigestible or poorly digestible food materials. He should remain refrained from all kinds of sexual activities and hard physical labor. He should remain abstained from sunlight, alcohol consumption and anger [5].

Preparations of Guggulu: There is a good number of Guggulu preparations described in Ayurvedic literature in various clinical conditions. But most of them have been described in pain and inflammatory conditions along with other clinical conditions. Some of the commonly used Guggulu preparations are Yogaraja Guggulu, Mahayogaraja Guggulu, Kanchanara Guggulu, Kaishora Guggulu, Gokshuradi Guggulu, Trayodashanga Guggulu, Triphala Guggulu *etc*. Out of these Kanchanara Guggulu is exclusively indicated in Gandamala (cervical lymphadenitis), Apachi(scrofula), Arbuda (cancer), Granthi (tumor), Vrana(ulcer), Gulma (abdominal tumors), Kustha (skin diseases) and Bhagandara (fistula in ano) [14, 15].

On the basis of evaluation of the properties, actions and indications of Guggulu and its compound formulations described in various classical texts of Ayurveda, it is evident that most of them have been prescribed for some common symptoms like pain, inflammation, chronic unhealed ulcers, tumorous swellings, Vidradhi (abscess) which are mostly the clinical features of various types of cancer.

In all the cases of Vata Vyadhi (neurological diseases), Vatarakta (gout) and Amavata (rheumatoid arthritis) pain and inflammation are the common features. Cancer itself is an inflammatory disease and is due to the over activation of the inflammatory pathway. Guggulu is also a Rasayana, so useful in the maintenance of the general health of the healthy individual as well as a cancer patient [14, 15].

Phytoconstituent of Guggulu: Guggulu contains volatile oil which contains monoterpenes, sesquiterpenoids, diterpenoids, triterpenoids. Other than terpenes the gum resin contains steroids, long chain aliphatic tetrols, aliphatic esters, ferulates, lignans, carbohydrates, amino acids and a variety of inorganic ions besides other unidentified constituents. Major steroidal constituents include E-guggulusterone, Z-guggulusterone, guggulusterone M, dihydroguggulusterone M, guggulusterol –Y, guggulusterol-I, II, III, IV, V, and VI, progesterone and related steroids. The Z- and E-guggulusterones are the main active compounds of the plant**.** The genuine samples of Guggulu contain not less than 1% of volatile oil and between 1.0 and 1.5 % of guggulusterones-(Z and E) [6].

Identity, Strength and Purity: Guggul produces not more than 5% of total ash and 1% of acid insoluble ash. It yields not less than 27 % of alcohol soluble extractive and not less than 53% of water-soluble matter. Ayurvedic Pharmacopoieia of India prescribes not more than 4% of presence of foreign matter in Guggulu. Drug occurs in vermicular or stalactitic pieces of pale yellow or brown colored mass, makes milky emulsion in hot water and readily burns, when fresh viscid and golden colored, odour-aromatic, taste-bitter and astringent [16].

Concept of Cancer in Ayurveda: Various clinical conditions mentioned under the context of Arbuda (tumors), Shotha (inflammations), Udara (enlargement abdomen including ascites), Gulma (various kinds of abdominal lumps/tumors), Granthi (glandular swellings), Apachi (cervical lymphadenitis), Vidradhi (abscess), Sthanaroga (diseases of the breast), Ostaroga (diseases of lips), Mukharoga (diseases of oral cavities), Asadhya Vrana (incurable or malignant ulcers) etc. resemble with the cancer of the respective organ. Out of them Arvuda apparently denotes tumors of malignant origin while Granthi apparently denotes tumors of benign origin [17, 18].

Etiopathogenesis of Cancer in Ayurveda: Cell division and metastasis are mainly controlled by Vayu while tumor formation and growth of the tumor is mainly controlled by both Vayu and Kapha. The Dushyas or the vitiated tissue elements are Rakta (blood), Mamsa (muscle tissues) and

Medodhatu (adipose tissues). There is also the involvement of down regulation of Agni/enzymatic actions (Mandagni) and derangement of Srotas (channels in terms of blood vessels and lymphatics) obstruction (Sanga) and abnormal transport (Vimarga Gamana/ invasion/metastasis) [17, 18]. Reported anticancer activities of Gum Guggal and its derivatives have been discussed below with special reference to their anti-cancer, anti-inflammatory, anti-oxidant, immune-modulating activities.

Anti-cancer Potential of Guggulu:

Breast Cancer: A group of investigators found that Gugulipid (GL) isolated from CW significantly inhibited growth of MCF-7, MDA-MB-231 breast cancer cell lines with an IC50~2 μM. The GL induced growth inhibition was correlated with apoptosis induction and evidenced by an increase in cytoplasmic histone associated DNA fragmentation and caspase-3 activity. The GL induced apoptosis was also associated with down regulation of the β-catenin signaling pathway. On the other hand, the normal human mammary epithelial cells HMEC compared to the breast cancer cells were significantly more resistant to growth inhibition and apoptosis induction by GL [19].

Another group of scientists found that combined therapy of gugulusterone (GS) (Farnesoid X Receptor (FXR) antagonist) and bexarotene (BEX) (retinoid X receptor agonist) (RXR agonist) increased doxorubicin (an anti-cancer anti-biotic) retention at the human breast cancer cells (MDA-MB-231) and augmented its cell death efficacy by more than 5 folds. The study suggested a novel mechanism by which GS and BEX combined therapy induced their anticancer activity. GS induced a sphingolipid named ceramide which subsequently induced the breast cancer resistant protein (BCRP) secretion as a result of which multi drug resistance of breast cancer cells to cancer chemotherapy is reduced. On this basis, investigators suggested that both GS and BEX may be useful as an adjuvant drug for sensitizing breast cancer cells and cancer stem cells to chemotherapy [20]. GS along with other natural compounds like curcumin, withaferin A, resveratrol etc was studied for their effect of DNA methyltransferase (DNMTs) enzyme which is over expressed in breast cancer cells. All the natural compounds including GS resulted in a significant decrease in the transcription levels of all the DNMTs in study. Importantly these natural compounds decreased the protein levels of DNMT1, HDAC1 (Histone deacetylase-1) and MeCP-2 (Methyl CpG binding protein -2). These natural compounds have been suggested to be used as potential candidates for chemoprevention in breast cancer [21]. Estrogen is a hormone which has been implicated in breast cancer. Estrogen works by binding to the estrogen receptors (ER). Over expression of estrogen hormone receptors by breast cancer cells makes them sensitive to estrogen therapy. The use of ER antagonists like tamoxifen, raloxifene, clomiphene is restricted due to a number of adverse effects. GS has been found to down regulate the expression of ERα in MCF-7 breast cancer (adenocarcinoma) cells. On the basis of these findings, the investigators suggested that GS could be a viable therapeutic alternative in the treatment of ER-positive breast cancer cells which are resistant to tamoxifen [22].

Pancreatic Cancer: Increased FXR (a bile acid receptor) expression has been confirmed in pancreatic tumors in comparison to adjacent tissues and high FXR expression has been found in lymphatic metastasis, enhanced migration, invasion and poor prognosis in pancreatic cancer. On the other hand, FXR inhibition is associated with reduced cell proliferation, migration and invasion in pancreatic cancer cell lines [23, 24].

GS is now widely recognized as a natural antagonist of FXR on the basis of available experimental evidence. The effect of GS on pancreatic cancer cell migration, proliferation and invasion was studied using DMSO as control on MIA-PaCa2 and PANC-1 (ductal epithelial) cell lines. The cells were treated with 5, 10, 20 μg GS or DMSO. GS was treated for a period of 48 hours. The relative fold migration and invasion values of GS treated cells were normalized against DMSO treated cells observed after 72 hours of treatment in a dose dependant manner [23]. Contrasting to the above, in pancreatic adenocarcinoma patients, simultaneous elevated expression of both FXR and RXR (α, β, γ) receptors expression has been associated with smaller tumor size, reduction or absence of lymph node metastasis, longer survival time of the patient with favorable prognosis and

less tumor aggressiveness [25]. A combined administration of GS along with the conventional chemotherapeutic agent Gemcitabine in pancreatic cancer cell lines has been found to increase the apoptotic cell death and growth inhibition in a synergistic manner when compared to treatment either with gemcitabine or GS alone. In addition, the tumors from xenografted mice in vivo showed a better antitumor response to GS and gemcitabine combination treatment compared to gemcitabine or GS alone. The investigators have found similar mechanism involved in both in-vitro and in-vivo anticancer effect of both the drugs through the down-regulation of NF- κB, Akt pathways and anti-apoptotic protein BcL-2 and through the activation of c-Jun NH(2)-terminal kinase and Bax in pancreatic cancer cell lines and nude mice xenograft [26].

A group of scientists using in vitro model have shown that GS prevents cell proliferation, inhibits cell motility, reduces cell invasion and induces apoptotic cell death in pancreatic cancer cell lines Capan1 and CD18/HPAF. The anti-cancer activity of GS was correlated with the downregulation of anti-apoptotic proteins, cell cycle progression proteins and up-regulation of pro-apoptotic proteins. Furthermore, the reduced motility and suppressive effects on invasion in pancreatic cancer cells by GS were associated with the disruption of cytoskeletal organization, inhibition of FAK and Src kinase signaling. GS treatment was also found to reduce mucin MUC4 gene expression by inhibition of JAK kinase mediated signaling [27]. GS also inhibited radiation induced NF-κB activation and enhanced radiosensitivity in the pancreatic cell line, PC-Sw. It reduced both cell cycle movement and cell growth by reducing IGF1-Rβ protein and inhibition of NF-kB in pancreatic cancer cells PC-Sw [22].

Head and Neck Cancer: In head and neck squamous cell carcinoma (HNSCC), GS treatment inhibited the proliferation of HNSCC by inactivating the smokeless tobacco and nicotine induced activation of NF-kB and STAT-3 signaling cascades. GS treatment of the HNSCC prevented the NF-kB activation and enforced its degradation resulting in the inhibition of inflammatory and angiogenic responses as well as progression and metastasis [28].

In another in vitro experiment treatment of human head and neck squamous cell carcinoma (HNSCC) cell lines with GS demonstrated dose-dependent decreases in cell viability with EC_{50} ranging from 5 to 8 μM. GS induced apoptosis and cell cycle arrest, inhibited invasion on its own. GS also enhanced the efficacy of erlotinib, cetuximab and cisplatin in HNSCC cell lines. GS induced decreased expression of both phosphotyrosine and total STAT-3 contributed to growth inhibitory effect. In a xenograft model of HNSCC, GS treatment resulted in increased apoptosis and decreased expression of STAT-3. *In-vivo* treatment with Guggulipid, resulted in decreased rates of tumor growth and enhancement of cetuximab's activity [29]. Recently it has been reported that combination of GS and bortezomib (a proteasome inhibitor) synergize the loss of clonogenic survival of UM-22B (head and neck squamous cell carcinoma cell line) cells. The combined effect was strikingly higher than the individual effects of either guggulusterone or bortezomib in the loss of clonogenic survival of UM-22B cells when treated with either drug for a period of 48 hours in comparison to control. It was suggested that the combined therapy induced caspase-3 activation and cleavage of PARP were responsible for the loss of clonogenic survival of UM-22B cells [30].

Skin Cancer: Both GS and Myrrhanone have been found to inhibit melanogenesis in B-16 murine melanoma cells by down-regulating the tyrosinase expression. Guggulsterone dose-dependently inhibited isobutylmethylxanthine (IBMX)-induced melanogenesis and cellular tyrosinase activity with no cytotoxicity. Decreased melanin biosynthesis was accompanied by the reduced expression of melanogenesis-related genes, such as tyrosinase, microphthalmia-associated transcription factor, tyrosinase-related protein (TRP)-1 and TRP-2 [31, 32].

Kidney Cancer and Cervical Cancer: Novel pyrimidine hybrids synthesized from chemically transformed Myrrhanone C, a bicyclic tri-terpenoid isolated from the gum resin of CW, evaluated for their antineoplastic potential against 6 cancer cell lines namely A-549(lungs), Hela (cervical cancer cell line), MCF-7(breast), ACHN (renal adeno-carcinoma cell line), COLO-205(colon cancer) and B-16 (mouse melanoma) by employing MTT assay. Synthesized compounds displayed significant

anticancer activity against all the cancer cell lines tested [32].

Esophageal Cancer: GS treatment to the Barett's esophagus derived cell lines was found to significantly reduce the over-expression of the bile acid receptors FXR in the Barett's esophagus cell lines. The investigators found a significant increase in apoptosis along with increased expression of caspase-3 activity [33]. In another study, a combination of amiloride and guggulusterone showed super-additive effects in suppressing esophageal cancer cell growth in vitro and in nude mouse xenografts. The study suggested that inhibition of NHE-1 gene (gastric acid inducing gene Na+/H+ exchanger-1) expression (which is highly expressed in esophageal adenocarcinoma) through combined administration of amiloride and GS could be useful in control of esophageal adenocarcinoma. The study also reported that even individual drug administration of either of them have the capacity to reduce the cell viability of the esophageal cancer cells. But the combined drug effect of GS and amiloride administered together is much superior to their individual effects [34]. In another study GS reduced cell viability, induced apoptosis in esophageal adenocarcinoma cells in vitro and tumor formation and growth in nude mouse xenografts through activation of caspase -3, caspase-8, and caspase-9 enzymes [35].

Colon Cancer: GS treatment has been found to possess anti-cancer activity against colorectal cancer *in-vitro* model. GS treatment to colon cancer cell line has been shown to block angiogenesis and metastasis by inactivation of STAT-3 activity and down-regulation of VEGF expression [36]. In another study GS significantly increased apoptosis in HT-29 cells by activating caspases-3 and -8 and down regulation of anti-apoptotic Bcl-2 group of proteins and activation of JNK kinase. The size of HT-29 xenograft tumors in guggulsterone-treated mice was significantly smaller than the size of tumors in control mice [37]. An *in-vivo* study has demonstrated that GS significantly reduced dextran sulfate sodium (DSS)-induced acute murine colitis as assessed by clinical disease activity score, colon length, and histology. Tissue upregulation of I-kappa-B and IKK phosphorylation induced by DSS was attenuated in guggulsterone-treated mice. Similar results were also reproduced by the same group of researchers with the in-vitro models in human Caco-2 (colorectal adenocarcinoma) cells and rat non-transformed Intestinal Epithelial Cells (IEC-18) stimulated by inflammatory molecules LPS (lipopolysachharide) and IL-1β. This effect was found due to GS-mediated down-regulation of NF-kB signaling pathway whose activation is associated with colitis and colon cancer. Guggulsterone also significantly reduced the severity of DSS-induced murine colitis as assessed by clinical disease activity score, colon length and histology. The study suggested that GS could be a potential therapeutic option in the treatment of irritable bowel disease (IBD) [38]. The effect of GS was studied in HT-29 colon cancer cells *in-vitro* and in HT-29 xenografted mice tumors *in-vivo*. GS significantly induced apoptosis in HT-29 colon cancer cells *in-vitro* by activating the caspase systems -3 and -8 along with decreasing the cIAP-1, cIAP-2, and Bcl-2 protein levels and increasing the levels of truncated Bid, Fas, p-JNK and p-c-Jun. In the *in-vivo* study, GS-treated mice had a significantly smaller size of HT-29 xenograft tumors in comparison to the size of HT-29 xenograft tumors in control mice (GS untreated). The authors suggested a potential therapeutic use of GS in the treatment of colorectal cancer [39].

Prostate Cancer: GS treatment of human prostate cancer cell line PC-3 resulted in the efficient cytotoxic effect by inducing apoptosis without affecting the normal prostate epithelial cells (PrEC) as observed by a group of scientists. This GS mediated apoptosis of PC-3 cells was correlated with the over expression of Bcl-2 family members such as Bax and Bak and sequential activation of caspase cascade [40]. The growth inhibitory effect of GS in prostate cancer has also been proposed to be due to inactivation of ATP citrate lyase (ACL or ACLY) which results in the inhibition of Akt signaling pathway which is being up-regulated in androgen resistant prostate cancer cells 41. On the other hand, treatment with GL (Gugugulipid) significantly inhibited the viability of cancer cells in human prostate cancer cell line LNCaP (androgen-dependent) and its androgen-independent variant (C81) with an IC (50) of ~1 μM after 24-hour treatment, at different concentrations standardized to z-guggulsterone. The GL-induced apoptosis was associated with reactive oxygen species (ROS) production and c-

Jun NH (2)-terminal kinase (JNK) activation along with the induction of pro-apoptotic Bcl-2 family proteins Bax and Bak and a decrease of Bcl-2 group of anti-apoptotic proteins in GL-treated cells. SV40 immortalized mouse embryonic fibroblasts derived from Bax-Bak double-knockout mice were significantly more resistant to GL-induced cell killing compared with wild-type cells. The investigators also observed that a normal prostate epithelial cell line (PrEC) was relatively more resistant to GL-mediated apoptosis compared to prostate cancer cells [42].

Liver Cancer: Sub toxic dose of GS and tumor necrosis factor related apoptosis inducing ligand (TRAIL), both induced apoptosis efficiently in hepato-cellular carcinoma (HCC) cells. The apoptotic mechanism induced by treatment with a GS/TRAIL combination involved the loss of mitochondrial trans-membrane potential and consequent activation of caspase group of enzymes [43].

Pathological accumulation of extracellular matrix proteins has been shown to be involved in liver fibrosis that can lead to precancerous cirrhosis of the liver. GS was found to have anti-fibrotic activity by inhibiting growth of immortalized LX-2 hepatic stellate cells (HSCs) via induction of apoptosis as it mediated reduced activation and survival of HSCs, which serve as the primary source of the matrix proteins. GS-induced apoptosis in HSC was accompanied by activation of c-Jun-N-terminal kinase and mitochondrial apoptotic signaling. GS-induced HSC growth inhibition was also found to involve Akt and adenosine monophosphate-activated protein kinase (AMPK) phosphorylation modifications resulting in the activation of pro-apoptotic proteins and down regulation of anti-apoptotic proteins. GS also inhibited NF-κB activation in LX-2 cells, which is one of the major mediators in HSC activation [44].

Lung and Ovarian Cancer: Few studies support the anticancer activity of GS in the lungs and ovarian cancer. Treatment with GS to the human lungs and the ovarian cancer cells resulted in the inhibition of cell proliferation and inhibition of Cyclin-D1 and cdc2 expression leading to inhibition of DNA synthesis. The investigators correlated GS mediated apoptosis with the activation of JNK, activation of caspase cascade and inhibition of the expression of various anti-apoptotic genes and inhibition of Akt pathway [45, 46]. Other than GS, Myrrhanone C, a bycyclic tri-terpenoid isolated from the gum resin of CW, has been chemically transformed to synthesize a series of ten novel pyrimidine hybrids and evaluated for their antineoplastic potential against 6 cancer cell lines namely A-549 (lungs), Hela (cervical), MCF-7(breast), ACHN (renal), COLO-205(colon) and B-16 (mouse melanoma) by employing MTT assay. Synthesized compounds displayed significant anticancer activity against all the cancer cell lines tested and specifically against lung cancer cell line A-549 [70].

Hematological Malignancies: These malignancies are classified into leukemia, lymphoma and multiple myeloma (MM) *etc*. GS has been reported for its anti-leukemic effect. Sishodia and colleagues reported that treatment of leukemia, myeloma and melanoma cell lines with GS resulted in decreased proliferation along with reduced level of cyclin-D1 and cdc-2 which inhibited the DNA synthesis. They found increased levels of cyclin dependent kinase inhibitor p21 and p27 as well as induction of apoptosis by activation of JNK, caspase cascade, PARP-cleavage and down regulation of anti-apoptotic products [45].

In another study, the antileukemic effects of three isomeric pregnadienedione steroids derived from GW gum resin including *cis*-guggulsterone, *trans*-guggulsterone, and 16-dehydroprogesterone were investigated in HL60 and U937 cells as well as in primary leukemic blasts in culture. All three compounds inhibited the proliferation of HL60 and U937 cells, with IC_{50} ranging from 3.6 to 10.9 µmol/L after treatment for 6 days via induction of apoptosis and differentiation [47].

Oral Cancer: A group of investigators studied the anticancer potential of dried extract of CW and z-GS on oral cancer cell lines (SCC-4, KB). Both CW and GS significantly inhibited tumor cell growth, caused cell cycle arrest and apoptosis in both tumor cells which were proposed to be due to inhibition of NF-κß, cyclin D1and restoration of p53 suggesting the role of CW and z-GS in oral cancer [48].

Cholangiocarcinoma (Bile Duct Cancer): The role of GS in cholangiocarcinoma was investigated along with its underlying mechanism of action by a group of researchers. The immortalized human cholangiocarcinoma Sk-ChA-1 and Mz-ChA-1 cell lines were treated with various concentrations of Z-guggulsterone, a *trans*- isomer of GS. Z-guggulsterone significantly inhibited the growth of the two human cholangiocarcinoma cell lines by inducing cellular apoptosis by the activation of caspases-3, -8 and -9 and by accumulation of cleaved poly-adenosine-diphosphate-ribose polymerase(PARP) along with, down regulation of survivin and Bcl-2 proteins [49].

Glioblastoma: Guggulsterone (GS), was employed to enhance effectiveness of novel Sonic hedgehog (Shh) inhibitor SANT-1 on glioma cell viability. SANT-1 alone failed to induce apoptosis in glioma cells. But it reduced the proliferation of glioma stem–like cells. But Guggulsterone when employed together with SANT-1 inhibited both Ras and NFκB pathway activity and sensitized the glioma cells to SANT-1 induced apoptosis. Guggulsterone induced ERK activation also contributed to Caspase-9 activation. SANT-1 targeted the stem like glioma cells while guggulusterone targeted the non-stem like glioma cells. Therefore, a combined administration of guggulusterone along with SANT-1 has been proposed by the authors for the treatment of glioma [50].

Anti-inflammatory and Immune-modulator Studies: There has been intense interrelationship between inflammation, cancer and immunity. Cancer is more related to chronic inflammation rather than acute inflammation which is self limiting in character because the production of anti-inflammatory cytokines follows the pro-inflammatory cytokines closely. However, chronic inflammation is due to persistence of the initiating factors, or a failure of mechanisms required for resolving the inflammatory response. Many cancers arise from sites of infection, chronic irritation and inflammation. Persistent infections within the host induce chronic inflammation. Leukocytes and other phagocytic cells induce DNA damage in proliferating cells, through generation of reactive oxygen and nitrogen species that are produced normally by these cells to fight infection. These species react to form peroxynitrite, a mutagenic agent. Hence, repeated tissue damage and regeneration of tissue, in the presence of highly reactive nitrogen and oxygen species released from inflammatory cells, interacts with DNA in proliferating epithelium resulting in permanent genomic alterations such as point mutations, deletions or rearrangements. P-53 mutations are seen in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. There is strong evidence of the association of inflammatory diseases with different cancers. Asbestosis and bronchitis are related to lungs cancer, cystitis with bladder cancer, gingivitis with oral squamous cell cancer and inflammatory bowel disease with colorectal cancer, chronic pancreatitis with pancreatic cancer and reflux esophagitis with esophageal cancer and so on [51].

Anti-inflammatory studies on Guggulu: The anti-inflammatory effect of the CW gum was studied in peripheral blood mononuclear cells (PBMC). Both crude ethyl acetate extract and the lead compound, thus isolated, showed inhibitory effect on proliferative response of PBMC in mitogenic lymphocyte proliferation and MLR assays. Further studies on inflammatory mediators such as IFN-γ, IL-12, TNF-α, IL-1β and NO showed down regulation, whereas no inhibition was observed in the case of anti-inflammatory cytokine IL-10 [52].

Guggulsterone(GS), has been investigated in two models of intestinal inflammation induced in mice by trinitro-benzene sulfonic acid (TNBS) and oxazolone. The results showed that GS protects mice against the development of signs and symptoms of colon inflammation. GS effectively attenuated the severity of disease, the fecal score and colon inflammation as assessed by measuring the macroscopic and microscopic damage scores. In vitro, mechanistic studies carried out using CD4+ cells isolated from the intestinal lamina propria demonstrated that GS effectively regulates the function of effector T cells. The net biological effects resulting from exposure to GS includes attenuation of the generation of IL-2, IL-4 and IFN-γ as well as T cell proliferation [53]. GS blocked the NF-κB signaling pathway and attenuated DSS-induced acute murine colitis [54]. Hexane-soluble portion of the MeOH extract of Guggulu yielded several cembrenoids (compounds

1-6), a bicyclic diterpene (copound 7), guggulusterone derivatives (compound 8-11), myrrhanone derivative (compound 12), myrrhanol derivative (compound-13) and a lignan (compound-14). These compounds were assayed for lipid peroxidation and cyclooxygenase (COX) enzyme inhibitory activities. Various derivatives from Guggulu like compounds 3 and 6 (combrennoid compounds), and compound 14 (a lignan) inhibited the lipid peroxidation by 79, 57, and 58%, respectively and the rest of isolated compounds showed 20-40 % inhibitory activity with respect to the control. In COX-1 and COX-2 enzyme inhibitory assays, compound 3 (combrenoid) showed 79 and 83%, and compound 8 (guggulusterone derivative) gave 67 and 54% of inhibition, respectively, at 100 ppm. All fourteen compounds inhibited COX-1 enzyme at 100 ppm and several of them also inhibited lipid peroxidation at the same concentration. This study reaffirms the antioxidant and anti-inflammatory potential of various compounds present in Guggulu [55].

Anti-inflammatory effect of phenylbutazone, ibuprofen, fraction A of Gum Guggul from CW were administered orally at a daily dose of 100, 200 and 500 mg /kg bw respectively for a period of 5 months. All the 3 drugs decreased thickness of joints during the course of drug treatment in experimental arthritis in right hock joint of albino rabbits by intra-articular injection of killed mycobacterial adjuvant in liquid paraffin. Development of this arthritic syndrome was studied for a period of five months with or without drugs [56].

Ethyl acetate fraction of the CW which is known in the name of guggulipid was tested for its topical anti-inflammatorty activity in a topical gel form known in the name of Emulgel. The gel containing the guggulipid shown significant anti-inflammatory topical effect in the caragennan induced rat paw edema and the effect was comparable to that of tacrolimus gel which was used as a standard topical anti-inflammatory agent [57].

A group of investigators had studied the anti-arthritic and anti-inflammatory activity of Gum Guggal and its various fractions in the Brownlee's formaldehyde induced arthritis in albino rats of either sex weighing 100±10 gms. The test fractions were administered in different doses in the form of emulsions in 5% gum acacia. All the fractions obtained from Gum Guggal with different organic solvents possessed a highly significant anti-inflammatory and anti-arthritic activity as compared to hydrocortisone and butazolidin as reference standards. The investigators proposed that the anti- inflammatory and anti-arthritic activity resides only in the oleoresin part, but not in the gum part up-to a dose of 40mg/kg [58].

Antioxidant Effect: The antioxidant activity of CW ethyl acetate extract was determined according to the thiocyanate method. Various concentrations (50, 100, 250 and 500 µg /ml) of the extract dissolved in distilled water were added to linoleic acid emulsions (2.5 ml, 0.04 M, pH 7.0) and phosphate buffer (2ml, 0.04M, pH7.0). The antioxidant activities were evaluated in terms of decreased lipid peroxidation and increased reducing power. Both these activities were dose dependant. At the above concentrations CW extract had a 31.99, 38.01, 45.46 and 51.16 % inhibition on lipid peroxidation while α-tocopherol at the concentrations of 500 µg /ml showed 76.38% inhibition of lipid peroxidation in linoleic acid system. However, these effects of CW were found to be lower than those of Gallic acid and α-tocopherol which were used as comparative and standard drugs respectively. At the same time α-tocopherol at the concentrations of 500 µg /ml showed 76.38% inhibition of lipid peroxidation. But the authors suggested that low antioxidant activity of CW does not necessarily indicate a low medicinal value or potency [59].

The antioxidant effect of Guggul and Guggulsterone has been demonstrated *in-vivo* in experimental rats. Nifedipine (a calcium channel blocker), propranolol (a beta blocker) and Guggulsterone were found to reverse both isoproterenol-induced cardiac necrosis in rats which were due to the elevation of pro-oxidant enzyme xanthine oxidase and lipid peroxidation and isoproterenol-mediated decrease of the antioxidant enzyme superoxide dismutase (SOD). Reversal of changes of lipid peroxide, xanthine oxidase and superoxide dismutase have been observed by these cardio-protective drugs in isoproterenol induced myocardial necrosis giving

rise to ischemia in rats [60]. Another mechanism through which guggulusterone (Z and E) reduces oxidative stress is through reduction of nitric oxide induced by bacterial lipopolysachharides (LPS) in macrophages with IC 50 value of 1.1 and 3.3 μM respectively [61].

It is generally accepted that overproduction of nitric oxide is associated with oxidative stress, which is involved in the pathogenesis of cardiovascular diseases, diabetes, rheumatoid arthritis, neurodegenerative diseases, chronic inflammation and cancer [62]. Recent evidence have shown that nitric oxide (NO) signaling is implicated in the pathophysiology of many types of cancer, particularly in tumoriogenesis and cancer progression in various tissues including the brain, breast, prostate, pancreas and lung [71, 72].

Clinical Studies: Majority of the clinical studies on CW have been conducted for its hypolipidemic, anti-inflammatory and anti-arthritic activities. Since cancer is a disease which is inherently associated with inflammation, citing these clinical trials will further supplement our claim and will focus upon the clinical efficacy of CW in various inflammation related clinical conditions in human subjects. Few of them have been cited below. The Guggulu(CW) and Pushkarmool (*Inula racemosa*) were administered in combination to 200 patients of ischemic heart disease provided relief of chest pain as well as improved functional status. Improvement in grades assigned at the pretreatment level for precordial pain and dyspnoea, restoration of normal ECG patterns, and significant reductions in cholesterol, triglycerides and total lipid levels indicate a beneficial effect of treatment with the combined drug [63].

In another study, the anti-inflammatory activity of Guggul was evaluated in 30 patients with arthritis in at least one knee. Gum Guggul at a dose of 500 mg three times daily for one month significantly improved the WOMAC (Western Ontario and McMaster Osteoarthritis Index) total score and continued to improve it at the 2-month treatment and follow-up. With the secondary measures of pain in the visual analog scales, patients exhibited significant improvement after 2 months of treatment. The results demonstrated the beneficial effect of the therapy in arthritic patients.

Although the study was focused on arthritis, the finding suggested the anti-inflammatory effect of Guggul therapy [64]. High-sensitivity C-reactive protein (hs-CRP), mainly synthesized in the liver in response to cytokine stimulation, is an index of inflammation that is now believed to directly promote all stages of atherosclerosis, including plaque rupture [65].

In a human clinical trial conducted in the United States, it was found that the median serum hs-CRP level was decreased by 29% in the group receiving gugulipid at a dose of 2000 mg daily, while the hs-CRP level was increased by 25% in the group receiving placebo during the trial period indicating the anti-inflammatory activity of gugulipid [66].

Side Effects and Drug Interaction: Guggulu has been used in Ayurvedic practice since thousands of years without any significant side effects. Clinical studies published in recent days report short-term use (less than 6 months), either of Guggul or of gugulipid is generally safe except occasional adverse reactions. Renal function, liver function, hematological parameters and electrolytes remained approximately unchanged. However, few adverse reactions like gastrointestinal discomfort including loose motion, mild nausea and hiccup have been reported. Skin rashes or hypersensitivity reactions have been reported in some clinical studies. In one study, 9% of participants developed moderate to severe adverse reactions within 48 hours of the initiation of the therapy [66, 67].

On the other hand, when Guggulu or guggulipid is concurrently administered with the β-blocker propranolol or calcium channel blocker diltiazem reduces the efficacy of both the drugs by decreasing their bioavailability thus confirming the drug interaction ability of CW [68]. In contrast to its hypolipidemic and cardioprotective activity, one study has suggested that Gugulipid causes hypercholesterolemia leading to endothelial dysfunction, increased atherosclerosis and premature death by ischemic heart disease in male mice suggesting its potential toxicity in the cardiovascular system in human being [69].

DISCUSSION: CW is an important Ayurvedic drug which has been used since centuries in the Indian systems of medicine. The drug has been

mainly used for pain and inflammatory conditions like osteoarthritis, rheumatoid arthritis, gout and other skeleton-muscular inflammations, chronic unhealed ulcers, cysts, scrophula, lymphadenitis, lymphangitis, obesity, diabetes, hyperlipidemia *etc*. The oleogumresin of the plant contains many chemical constituents out of which Guggulusterone Z and E are the most active constituents. Ethyl acetate extract is marketed in the name of Guggulipid containing both Z and E guggulusterones. In Ayurveda CW has been used for clinical conditions similar to various types of cancer or secondary to cancer. Keeping these traditional uses of Guggulu in mind, a review of literature was carried out in order to compile the anti-cancer studies available on CW.

Since, inflammation, immunity and cancer are deeply interrelated, a brief review on this axis of drug action has also been included in the study in order to understand the complete mechanism of action of CW on cancer. It is interesting to note that adequate number of anti-cancer research has been carried out on CW in various *in-vivo* and *in-vitro* models in various types of cancers. Most of the studies have taken guggulipid and guggulusterone as the active ingredient. Guggulusterone is the most active agent with anticancer activity in many cancer cell lines including hematological, colo-rectal, head and neck including oral, glioblastoma, pancreatic, lungs, ovarian, prostate, breast, esophageal, cervical cancers. Most commonly, it is the downregulation of the NF-kB pathway which mediates its anti-cancer and anti-inflammatory potential. Other inter-cellular communication pathways included inhibition of Akt, STAT-3 and β-catenin pathways.

The resultant effect of this inhibition is either induction or increase in apoptosis or cell cycle arrest or both. Both GS and GL up-regulate the pro-apoptotic proteins Bim, Bik and NOXA in various cell lines. GS has now been widely recognized as a natural FXR antagonist. FXR up-regulation is found in pancreatic, esophageal, breast and lungs cancers while it has anti-tumor effect on colorectal, liver and gall bladder cancers. In addition to the other mechanisms, GS inhibits cell proliferation by inhibiting the FXR up regulation. This is perhaps the principal mechanism of action reported how GS works in pancreatic and esophageal cancers with additional mechanisms in lungs and breast cancers. Both GL and GS not only possessed anti-cancer activities when administered alone, but also synergise the anti-cancer activity of various cytotoxic drugs like gemcitabine, tamoxifen, ebortezomib, erlotinib, cetuximab and cisplatin which gradually develop resistance to various types of cancer cells. They enhance the sensitivity of the cytotoxic drugs at their receptor levels in addition to their direct cytotoxic activity. These references suggest that both GS and GL can be used individually or as compound formulations or along with other conventional cytotoxic drugs during chemotherapy not only to produce cytotoxic effects but also to synergise the efficacy of these drugs along with antagonizing the adverse effects produced by these drugs.

Excessive generations of endogenous free radicals and high exposure to exogenous free radicals have been known to produce DNA damage inducing mutations in different cancer related genes. Although the benefit of exogenous supplementation of natural antioxidants in both cancer and cancer prevention is inconclusive, over-activation of oxidative pathway has been implicated in cancer. Guggulu has been studied in various oxidative stress models and has exhibited antioxidant activity. Thus, it can help prevent the DNA damage caused by reactive oxygen species. Similarly, the anti-inflammatory activities of Guggulu are mainly due to the inhibition of COX molecules and NF-kB pathway along with modulation of various pro-inflammatory cytokines and induction of anti-inflammatory cytokines which also partly explains the immune-modulatory role of the drug.

CONCLUSION: Cancer related traditional uses of Guggulu have been justified by the citation of various preclinical and clinical studies. Interestingly in the preclinical models CW has been found to induce cell death and apoptosis in more than 15 different types of cancer cell lines. Although many clinical studies are conducted to support the hypolidemic, anti-inflammatory action of CW, hardly there is any clinical trial report available in cancer patients. The present clinical trials have been mainly conducted on various inflammatory conditions like arthritis, hyerlipidemia, artherosclerosis and various types of skeletomuscular inflammations. But this is also an

admissible fact that CW has been used in inflammatory and cancer related conditions for a long time in Ayurvedic practice. Therefore, the present study suggests the indication of Guggulu in all types of cancers on the basis of Ayurvedic literature and reported modern preclinical and clinical studies. Again, the study suggests the drug to be used either in the purified oleo-gum resin form or in the form of Guggulipid (ethyl acetate extract fraction) in dose of 0.5gm to 2gms twice or thrice daily as most of the studies have been conducted only on purified Guggulu or its derivatives like Guggulipid (standardized to 2-7% of guggulusterone) specifically for anti-cancer purpose. If guggulusterone is used alone, the dose should be 25 to150 mg twice or thrice daily keeping 2-7 % content of guggulusterone in view in the standardized Gugulipid. However, Ayurveda mentions various compound formulations like Yogaraja Guggulu, Mahayogaraja Guggulu, Kanchanara Guggulu *etc* which contain a good proportion of Guggulu as their active ingredient. These compound formulations have been in Ayurvedic practice for centuries.

The activity of these compound formulations in cancer patients cannot be ruled out as Guggulu is the main active ingredient of these compound formulations. However adequate scientific data are not available to support the anti-cancer activity in accuracy of these compound formulations. In compound formulations bioavailability of the drug may be altered as Guggulu is mixed with other drugs. These additional drugs may have agonistic or antagonistic activities on the Guggulu binding receptors. Therefore, to get concrete anti-cancer results the study suggests purified Guggulu and its derivative drugs to be used alone with their vehicles described in Ayurved.

The preferable vehicles should be warm water, milk or Triphala (fruits of *Emblica officinalis, Terminalia chebula, Terminalia belerica* in equal quantities) decoction. The study also recommends controlled clinical trials on Guggulusterone, Guggulipid, purified Guggulu and the compound formulations of Guggulu in all the above categories of cancer on which CW has shown inhibitory activity in both *in-vitro* and *in-vivo* studies. This study entrusts the most possible therapeutic role of Gum Guggal in the treatment of various types of cancers on the basis of literature based pharmacological and clinical evidence analysis.

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