REVIEW

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HERBAL TREATMENT OF VIRAL CANCER

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ABSTRACT

Viral Cancer is one of leading cause of death worldwide. Viral cancers included liver cancer, anal cancer, oral, neck and head cancer etc. World health organization stated that 11.9% of human cancer is caused by one of the seven viruses. In most developed countries of world, viral cancer is big issue; however, notable improvements have been made in development of medical treatment and early detection of the disease over the last thirty years and surviving rate of the patients have been improved. Herbal medicine consists of plant extract or different mixtures of plant extract to cure disease and promote better health. Herbal drugs from natural compounds are preferred than allopathic due to their less side effects. Here attempt has been made to compile the medicinal plants having antiviral cancer activity. The bibliographic study is carried out to collect the material from internet source, review papers, text books and from original research papers. Many medicinal plants and their isolated compounds have been evaluated against viral cancers such as Artemisinin from *Artemisia annua*, Berberine from *Coptidis rhizoma*, Curcumin from *Curcuma longa*, Gambojic acid from *Garcinia hanburyi* and Geinstein from *Hydrocotylesibthorpioides* etc. The present literature will play essential role in the search of novelcompounds for viral cancer treatment and further studies should be carried out on thementioned medicinal plants.

Keywords: Medicinal plants, viral cancer, occurrence, phytoconstituents

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INTRODUCTION

Tumor virus or cancer viral cancer occurs worldwide. It is estimated that 1.9 million cases of cancer are to be caused by infectious agents including 17.8% of all cancers. 12.1% is related to viral infectious agents. About 12% of human carcinoma is caused by Onco viruses. Onco viruses are obligatory but not enough for the incidence of cancer therefore many years are required for its prevalence after severe infection. According to Hallmarks, cancer is biological outcome of oncogenic adaptation. Mutations result in the inactivation of Rasonco gene, formidable activator of protein MPAK and PI3K- AKT-mTOR cascades, ultimately form a tumor cell. Mutations actually immobilize the P 53 suppressorthat allow unrestricted growth of cells genetic vulnerability hallmarks (2). Unforced mutations and mutations by subjection to carcinogenic chemicals cause somatic oncogenic variations which are also known as oncogenic hits (3).

METHODOLOGY

Conventional text books and database such as Scopus, Web of science, Pub Med were searched for scientific literature published till 2018. The following terms used such as cancer,occurrence of viral cancer

Herbal treatment of viral cancer

A large number of herbs are widely used nowa day for the treatment of viral cancers. The interactions of drugs and herbs could be recalled thousands of years when herbs are mixed with one another for the formation of better drug.

Genistein

Hydrocotyle sibthorpioides is the main source of the Genistein. It is an isoflavone and ponders to be powerful chemoprotective agent against breast cancer with estrogenic actions (4). Level of inflammatory mediators is low when they are treated with genistein,

comprising myeloperoxidase, TNF-α and IL-6, through downstream regulation of CCl4-induced liver proliferation in rats and NF-κB in alcohols (5). The combination of tamoxifen and has antiproliferative effect on malignant breast cells. This is an important medical application in treating mammalian dysphasia because currently there is no chemopreventive treatment available. For treatment of breast cancer in women it may be an effective therapy (6). Genistein is also used for the treatment of liver cancer. Genisteinis also called phytoestrogen and angiogenesis.

Salvianic acid A

Salvianic acid A is widely used as natural product in the china. *Salvia miltiorrhiza* (Danshen) has the main active component Salvianic acid A. Fibrosis of HSCs is inhibited when we treat it with salvianic acid A, thus suppress the expression of TGF-β1 and collagen I/III. Stopage of plasminogen activator due to decrease in the level of TGF-β1 lead to, dephosphorylation of ERK1/2 &Akt and upstream regulation of the urokinasetypeplasminogen activator (7).

Helioxanthin

Shrub *Taiwania cryptomerioides* (Taiwan Shan) is the main source of the helioxanthin. In Lamivudine-resistant HBV L536M/M550V double mutant HBV strain and HepG cells helioxanthin show powerful inhibitory effect against HBV replication. IL-1-induced c-jun transcription and C-jun-mediated DNA-binding activity of AP-1 is suppressed when we treat with helioxanthin.One study shows that the binding ability of hepatocyte nuclear factors 3 & 4 to the machinery of HBV replication is suppressed by synthesized derivative of helioxanthin so suppressing the HBVduplication (8).

Galic Acid

Gallic acid stops multipication of cervical cancer cells.

A BrdU incorporation assay was performed with 15, 12.5 and 10 µg/ml of gallic acid treated with the HTB 35 and HeLa cells for 24 hours to make clear whether gallic acid participate to the inhibition of cell multiplication. Percentage of BrdU positive HTB 35 cells was reduced from29% of the control group to 3.3% with the help of gallic acid. Gallic acid stops the angiogenesis. Angiogenesis is a process in which new blood vessels are formed, which leads to the formation of solid tumors. Recent studies examined whether gallic acid have the capability to stop angiogenesis in HUVECs due to the neovascular nature of cervical cancer (9, 10). The untreated control group was consisting of multiple cells that collected together and attached to each other. Enlargement of the tubes at all levels is significantly inhibited by gallic acid and reducing the tube length per area to ~16.5, 15.3 and
30.3 percent respectively of the control group. Ginsenoside Rg5 is a main bioactive component that causes apoptosis of the cancerous cell.

Gambogic acid

Garcinia hanburyi is the main source of the Gambogic acid. Gamboic acid is a xanthonoid. Garcinia hanburyi is evergreen tree, small to medium-sized and smooth grey bark. Main activecomponent of gamboges is gambogic acid. Gamboges are resin obtained from different Garcinia species including the *Garcinia hanburyi* Hook.f (11). Gambogic acid has many biological impact, such as analgesic, anti-inflammatory and anti-pyretic also having anti-cancer actions (11). Many *In vivo* and *In vitro* studies have shown that gambogic acid is a powerful toxin against different malignant tumors, including glioblastoma and cancers of the breast, liver and lung. In China, recent clinical trials are conducted on gambogic acid (12, 13). Mechanism of action of gambogic acid is not clear. Gambogic acid induces apoptosis in different cancer cells.

Primary target of Gambogic acid is Transferrin receptor (TfR) that is over expressed in different cancers cells.

Gambogic acid binds independently to TfR instead of transferrin binding site, hence leading to the quick death of cancerous cells (14). Another molecular target of gambogic acid is stathmin; thisis revealed by proteomic analysis (15). Many otheranti-cancer targets, like nuclear factor kappaB (NF-_B) and topoisomerase IIa is influenced by gambogic acid (16). Anti-cancer activity of the other compounds increased by combiningthem with gambogic acid (15, 17). Furthermore, combination of celastrol and gambogic acid with Tca113 cells inhibit proliferation and induces apoptosis, it indicates that the combination of celastrol and gambogic acid can be beneficial for the treatment of oral squamous cell cancer. Another study showed that inhibition of tumors cell in humans and rate of apoptosis increasesin human gastric cells (BGC-823) when the 5- fluorouracil (5-FU) combined with gambogic acid (15). Furthermore, lower concentrations induced cytotoxicity in docetaxel-resistant BGC-823/Doc cells (17). Apoptosis and gambogic acid-induced cytotoxicity is enhanced in human leukemia cells (K562) with the help of nano magnetic particles like nano magnetic particles of(MNPs-Fe3O4) Fe3O4 (18).

Curcumin

Curcuma longa has a major active flavonoid that is curcumin (19). Discriptive studies shows that cancers prevalence is low in India thanother parts of the world due to frequent use of curcumin, suggested that curcumin intake is beneficial in cancer prevention (20). Many studieshave also shown that in breast cancer, prostate cancer, gastric cancer, colon cancer, leukemia, lymphoma and melanoma, curcumin inhibits cell proliferation (21). Curcumin enhances cell death with the help of many complex extrinsic and intrinsic pathways. Curcumin binds to different protein targets more than 30 including [epidermal growth factor receptor

(EGFR) transcription factors (NF-_B and activator protein-1), growth factor receptors [human epidermal growth factor receptor 2 (HER2), kinases [mitogen-activated protein kinase (MAPK) and PKC, protein kinase A (PKA),], cell cycle-related proteins (p21 and p53), inflammatory cytokines [tumor necrosis factor (interleukins and TNF)], urokinase plasminogen activators (u-PA) and matrix metalloproteinases (MMPs) (21, 22). Metastasis in medulloblastoma, lung, colon, and breast cancers is suppressed by oral intake of curcumin. The metastatic proteins regulation, such as intercellular adhesion molecules and MMP-9, MMP-2, vascular endothelial growth factor (VEGF) (23, 24). To check the tolerance, pharmacokinetics, efficacy of curcumin, safety and its combination therapy with present day anti-tumors drugs clinical trialsare conducted (25). Clinical trials are now a days conducted on curcumin to check its efficacy, tolerance, pharmacoline and safety. In clinical trial phase I, it was found that oral dose of 8g/day has no side effects in patients that intake the curcumin. In most treated patient improvement inclinical and biological responses were shown (26).

Berberine

Coptidis rhizoma (Huanglian) is the source of Berberine and it is an isoquinoline alkaloid. It is obtained from a Chinese medicinal herb. Berberine is used for detoxification and heat dissipation. Berberine having a dry weight consistupto 7.1 mg in 100 mg (27). Due to its antibacterial and anti-inflammatory activities, it is widely used as gastrointestinal drug in China (28). It is evident by many studies that berberine also has anti-cancerous results on tumor cells. p53, NF-_B, DNA topoisomerases, mitochondria, DNA or RNA etc are the multiple target site of berberine. Berberine exerts its cytotoxic effect and bind to polymorphic or oligonucleotides nucleic acid and stabilize G-

quadruplexes or DNA triplexes andthus inhibits telomerase and topoisomerase in cancerous

cells (29, 30). Hill model of cooperative interactions quantified electrostatic interactions between berberine and the cancerous cells (31).

Artemisinin

Chinese medicinal herb *Artemisia annua L* (Huanghuahao) has an active terpene that is Artemisinin. In China, it is used for the treatmentof malaria and fever. ARTs, such as artesunate anddihydroartemisin (DHA) anti-cancer activities both *in vivo* and *in vitro* (102-105). Major metabolites of artemisinin is dihydroartemisinin and semi-synthesized derivative of artemisinin is artesunate; both substances show anti-tumor potency. Anti-tumor power of artemisinin had beendetailed

investigated in different cancer cells, comprising cancer cells of breast, liver, lung and colon, ovary, pancreas and especially in leukemia cells. The expression of many different molecules such as g-glutamycysteinesynthetase(GLCLR), EGFR, c-MYC, cdc25A is related to selective anti-cancer potential of artemisinin. Artesunate or DHA also has anti-tumor activity against pancreatic cancer xenografts (32, 33). Artemisininstops angiogenesis (a process in which new blood vessels form from existing blood vessels) an important process of metastasis. Dihydroartemisinin (DHA) lowers the levels ofmain two VEGF receptors on HUVEC. It also stops angiogenesis of chorioallantoic membrane at lower concentrations (34). VEGF secretion and expression in chronic myeloid leukemia K562 cells is stopped when conditioned media from K562 cells pretreated with Dihydroartemisinin, leading to angiogenetic activity slow down (35). The expression of avb3 integrins and MMP2 the in human melanoma cells is decreases due to inhibition of cell migration and concomitantly by artemisinin, Levels of

MMP2,u-PA, MMP9 and MMP7 is related to metastasis which is regulated by artemisinin (36).

Thymoquinone

The anti-tumor action of thymoquinone (TQ) looks promising both for chemoprevention and preventing drug-induced side effects. Mouse keratinocytes and normal human pancreatic ductal epithelial cells (HPDEs) show resistant to the apoptotic effects of thymoquinone. Thymoquinone also have anti-inflammatory effect on pancreatic ductal adenocarcinoma (PDA) cells, and these processes are paralleled by inhibition of NF _B (37). Thymoquinone stops growth of cancer in nude mice with the help of xenograft prostate tumor model. This was correlated witha reasonable decrease in transcription factor E2F-1, cyclin A and androgen receptor as known by Western blotting method. All studies and findings show that Thymoquinone may prove to be beneficial agent in curing hormone-refractory prostate cancers and hormone sensitive cancers.

Wogonin

Scutellaria baicalensis Georgi (Huangqin) is the main source of Wogonin. Wogonin dry weight consists of upto 0.39 mg in 100 mg (38).Inflammatory diseases has been cured by usingwogonin. It also causes reduction of (COX-2) cyclooxygenase-2. It induces apoptosis through the inhibition of NF-_B, shifting O2- to H2O2 and mediation of Ca2+ to some range; H2O2, activates phospholipase Cg by serving as signaling molecule (39). Furthermore, wogonin induces cell type dependent cell cycle inhibition in human cervical carcinoma HeLa cells observed at the G1 phase and in THP-1 cells at the G2/M phase(40).

Etoposide is a drug on which synergistic effect of ogonin is checked. Etoposide-

induced apoptosis (cell death) in tumor cells is improved with the help of Wogonin. Significantly, typical P-glycoprotein (P-gp) inhibitors verapamil and cyclosporine A induced apoptosis in similar way as the wogonin (41, 42). Other P-gp substrates like vinblastine and doxorubicin, do not exhibit anysynergistic effect (43). Similar effect was observedwhen wogonin is used with 5-FU in MGC-803 transplanted nude mice and human gastric MGC- 803 cells. The underlying mechanisms might bedue to its inhibition of NF-kB nuclear translocation activity and pro-apoptotic effect. Anti-viral and anti-inflammatory action of wogonin may also participate to cancer prevention. Wogonin is proved assurance agent also good anti-tumor drug because of its large harmfulness to differenttypes of cancerous cell lines and the fewer sideeffects to healthy cell, as also having synergisticeffects.

Flavonoids

Flavonoids are polyhydroxyphenols. In plants,the role of flavonoid is pigmentation, UV filtration, and nitrogen fixation. The dietary sources of flavonoids are black tea, citrus, blue berries and wine. Flavonoids also have anti-oxidant and anti- inflammatory activity. Flavonoids contents are examined in mostly plants and how it effectson cancer cells are also studied. For example, fern species and litchi leaf are used in Chinese medicine (47). Dryopteriserythrosora is a fernspecies have an anticancer effect on human lung cancer (48).

Brassinosteroids

Brassinosteroids belongs to the six class of plant hormone. Brassinolide was firstly isolated brassinosteroid in 1979. It plays important role in cell elongation, cell expansion, polle

n elongation,and signal transduction. Mostly two natural brassinosteroids such as 24-epibrassinolide (24-epiBL) and 28-homocastasterone (28-homoCS) (49). Due to anticancer activity of brassinosteroid, these compounds give dissimilar reaction along with cancerous cells (50).

Polyphenols

The important resources of polyphenols are green tea, vegetables, fruits, red wine, black tea, and coffee etc. Polyphenolic compounds help to maintain proper metabolic function of the cell due to its antioxidant activity by regulating specific metal chelation reaction. Polyphenol compounds contain tannins, resveratrol,curcumin and gallacatechins and these all are anticancer compound (44). Curcumin is obtained from rhizome of curcuma inhibit cancer and have chemo-sensitizer effects longa which results inthe activation of other factor against cancer (45). The most occurring polyphenol is tannins and is found mest of plants. The antioxidant property andcytotoxic effect of polyphenols on cancerous cell has been revealed and determined (46). Rhizomeof ginger is used in mostly Chinese medicine against cancer, which is a phenolic complex (45).

Alkaloids

Alkaloids are commonly found in nature and mostly used in pharmaceutical industry. Alkaloids which are extracted from several herbs show anti metastasis and anti-proliferation effect on cancerous cell. Vinblastine and vincristine which are alkaloids act as an anti-tumor (15). Matrine isa dominant alkaloid and control pancreatic tumor (51). Similarly, piperine is also an alkaloid and it control breast stem cell to proliferate and does not effect on other cells (52).

Lectins

These are carbohydrate binding proteins and occurs in bacteria, fungi, plants and animals. Lectins acts against tumor due to its capability to distinguish unusual glycosylation arrangement outside the membrane of cancerous cells (53, 54). Moreover, death of cancerous cells can

promote by a mechanism which is triggered bythe precise binding of lectins with cancerous cells(55). In 1960, cancer therapy with the help of plantlectin was increased, after this researcher found

that mitotic division in lymphocytes was activatedby the *Phaseolus vulgaris* agglutinin (PHA) (56).

Broccoli

Broccoli is used to cure bladder cancer due to its anti-oxidant activity. A dietary element of broccoli which is called sulforaphane can reduce the mammospheres accumulation in human breast cancerous cells. Cancer and degenerative diseases can be prevented with the help of broccoli; it can also be used to curecardiovascular disease (57).

Aloe Vera

Aloe vera is a green color plant and found inall over the world, cultivated for agriculture and medicinal use. Aloe vera is used in traditional medicine for many years ago and it was mostly used for the treatment of breast cancer and lung cancer. In breast cancer patient who go through radiotherapy, Aloe vera was studied in detailed (58). In women who has breast cancer and go through for the treatment Aloe vera also investigated for its possessive effect but the investigation has controversy (59). When mild soup is combined with Aloe vera gel, mitigates dermatitis in breast cancer patient women who undergoing radiation treatment (58)

Withania somnifera

These are small shrubs with dark green leaves and orange color ripe fruit. Ashwagandha is usedfor the cure of many diseases from decades,numerous parts of this herb was useful in the cure of many types of cancers (60). The effectivepart of Ashwagandha are secondary metabolites aresaponin, alkaloids and lactones (61). Leaves of Ashwagandha have anticancer activity whileits berries have used to make cheese. We found with the help of cell based assay that cancer cell cytotoxicity was enhanced by Ashwagandha leaves extracts (62). Ashwagandha also have anti-oxidant and anti-inflammatory activity.

Ashwagandha extract and its components have anti angiogenic and anti-metastasis action (61). Ashwagandha is effective as immunomodulator, anti-tumor in brain cancer, fibroids, uterine tumor, sarcoma and endodermal carcinomas (60).

Milk Thistle

It belongs to family Asteraceae. This is the nativeherb of southern Europe and has purple flower andgreen leaves. Now it is found all over the world. Milk thistle is mostly used for the treatment of liver cancer. Along with the reduction of lipogenesis, silibinin was used to target pro-inflammatory markers which are derived from the seeds of milkthistle (63). Milk thistle was popularized on internet for its pretended capability to control many typesof cancer. Cancer research UK examined that there was no better evidence in this favor (64). Milk thistle is used for many other liver disorders.

Green Tea

It belongs to family Theaceae. Green tea originates in china. Extracts of green tea were used in Chinese and Indian herbal medicine (65).There are unambiguous confirmations that greentea is beneficial to control and cure the cancer in people (66).

Green tea has been used for many types of cancer like lung cancer, colon cancer, gastric cancer and breast cancer etc.

Soybean

It belongs to family Fabaceae. This herb is the

cheap source of protein and easily available. This soybean has biological activities counter to cancer (67). Saponin and phytic acid are the phenolic compounds of soybean and the anticancer activity of soya bean depend on these phenolic compounds (68). Newly studies exhibited that MMP-9 in the cells of colon cancer can also prohibited by the protein portion of soybean (69).

Skull Cap

Skull Cap belongs to family Lamiaceae. This herb is found in Asia. It is used mostly in traditional Chinese medicine. Laboratory studies have shownthat the extract of skull cap can affect apoptosis in prostate cancerous cells (70). It is mostly used forthe treatment of lung and intestinal cancer.

CONCLUSION

Medicinal plants will play important role in the management of viral cancer in near future. The medicinal plants mentioned in the review showed the ability to decrease the prevalence of viral cancer. These can be used as adjuvant with viral cancer managements. Information that is provided will basically help to design new drug formation in coming future.

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