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 *Hydrocotyle sibthorpioides* etc. The present literature will play essential role in the search of novel compounds for viral cancer treatment and further studies should be carried out on the mentioned medicinal plants.

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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 a 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 suppressor that 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). Each virus is related to specific type of cancer.

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, prevalence of viral cancer, medicinal plant having anticancer activity without restriction on the language of articles and without limiting the search articles.

Herbal treatment of viral cancer

A large number of herbs are widely used now a days 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 urokinasetype plasminogen 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 HBV duplication (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 from 29% 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 active component 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; this is revealed by proteomic analysis (15). Many other anti-cancer targets, like nuclear factor kappa B (NF-_B) and topoisomerase IIa is influenced by gambogic acid (16). Anti-cancer activity of

the other compounds increased by combining them 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 increases in 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 than other parts of the world due to frequent use of curcumin, suggested that curcumin intake is beneficial in cancer prevention (20). Many studies have 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 trials are 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 in clinical 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 consist upto 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 and thus 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 treatment of 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 been detailed 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). Artemisinin stops angiogenesis (a process in which new blood vessels form from existing blood vessels) an important process of metastasis. Dihydroartemisinin (DHA) lowers the levels of main 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 with a 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 using wogonin. 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 wogonin 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 any synergistic effect (43). Similar effect was observed when wogonin is used with 5-FU in MGC-803 transplanted nude mice and human gastric MGC-803 cells. The underlying mechanisms might be due 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 different types of cancerous cell lines and the fewer side effects to healthy cell, as also having synergistic effects.

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 in the activation of other factor against cancer (45). The most occurring polyphenol is tannins and is found mest of plants. The antioxidant property and cytotoxic effect of polyphenols on cancerous cell has been revealed and determined (46). Rhizome of ginger is used in mostly Chinese medicine against cancer, which is a phenolic complex (45).

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 effects on cancer cells are also studied. For example fern species and litchi leaf are used in Chinese medicine (47). Dryopteriserythrosora is a fern species 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, pollen 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).

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 is a 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 by the precise binding of lectins with cancerous cells (55). In 1960, cancer therapy with the help of plant lectin was increased, after this researcher found that mitotic division in lymphocytes was activated by 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 cure cardiovascular disease (57).

Aloe Vera

Aloe vera is a green color plant and found in all 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 used for the cure of many diseases from decades, numerous parts of this herb was useful in the cure of many types of cancers (60). The effective part of Ashwagandha are secondary metabolites aresaponin, alkaloids and lactones (61). Leaves of Ashwagandha have anticancer activity while its 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 native herb of southern Europe and has purple flower and green 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 milk thistle (63). Milk thistle was popularized on internet for its pretended capability to control many types of 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 green tea 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 is also used in medicinal herbs for the treatment of cancer. More famous 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 shown that the extract of skull cap can affect apoptosis in prostate cancerous cells (70). It is mostly used for the 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.

REFERENCES

1. De Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. The lancet oncology. 2012;13(6):607-15.
2. Mesri EA, Feitelson MA, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. Cell host & microbe. 2014;15(3):266-82.
3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. cell. 2011;144(5):646-74.
4. Huang Q, Huang R, Zhang S, Lin J, Wei L, He M, et al. Protective effect of genistein isolated from Hydrocotyle sibthorpioides on hepatic injury and fibrosis induced by chronic alcohol in rats. Toxicology letters. 2013;217(2):102-10.
5. Li Y, Zhang T, Korkaya H, Liu S, Lee H-F, Newman B, et al. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. Clinical Cancer Research. 2010:1078-0432. CCR-09-2937.
6. Tanos V, Brzezinski A, Drize O, Strauss N, Peretz T. Synergistic inhibitory effects of genistein and tamoxifen on human dysplastic and malignant epithelial breast cells in vitro. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2002;102(2):188-94.
7. Szuster-Ciesielska A, Kandefer-Szerszeñ M. Protective effects of betulin and betulinic acid against ethanol-induced cytotoxicity in HepG2 cells. Pharmacol Rep. 2005;57(5):588.
8. Ying C, Li Y, Leung C-H, Robek MD, Cheng Y-C. Unique antiviral mechanism discovered in anti-hepatitis B virus research with a natural product analogue. Proceedings of the National Academy of Sciences. 2007;104(20):8526-31.
9. Di SL, Caschetto S, Garozzo G, Nuciforo G, Cassaro N, Meli M, et al. Angiogenesis as a prognostic factor in cervical carcinoma. European journal of gynaecological oncology. 1998;19(2):158-62.
10. Triratanachat S, Niruthisard S, Trivijitsilp P, Tresukosol D, Jarurak N. Angiogenesis in cervical intraepithelial neoplasia and early staged uterine cervical squamous cell carcinoma: clinical significance. International Journal of Gynecological Cancer. 2006;16(2):575-80.
11. Panthong A, Norkaew P, Kanjanapothi D, Taesotikul T, Anantachoke N, Reutrakul V. Anti-inflammatory, analgesic and antipyretic activities of the extract of gamboge from Garcinia hanburyi Hook f. Journal of ethnopharmacology. 2007;111(2):335-40.
12. Wu Z-Q, Guo Q-L, You Q-D, Zhao L, Gu H-Y. Gambogic acid inhibits proliferation of human lung carcinoma

SPC-A1 cells in vivo and in vitro and represses telomerase activity and telomerase reverse transcriptase mRNA expression in the cells. Biological and Pharmaceutical Bulletin. 2004;27(11):1769-74.
13. Qi Q, Gu H, Yang Y, Lu N, Zhao J, Liu W, et al. Involvement of matrix metalloproteinase 2 and 9 in gambogic acid induced suppression of MDA-MB-435 human breast carcinoma cell lung metastasis. Journal of molecular medicine. 2008;86(12):1367.
14. Kasibhatla S, Jessen KA, Maliartchouk S, Wang JY, English NM, Drewe J, et al. A role for transferrin receptor in triggering apoptosis when targeted with gambogic acid. Proceedings of the National Academy of Sciences. 2005;102(34):12095-100.
15. Wang X, Chen Y, Han Qb, Chan Cy, Wang H, Liu Z, et al. Proteomic identification of molecular targets of gambogic acid: role of stathmin in hepatocellular carcinoma. Proteomics. 2009;9(2):242-53.
16. Pandey MK, Sung B, Ahn KS, Kunnumakkara AB, Chaturvedi MM, Aggarwal BB. Gambogic acid, a novel ligand for transferrin receptor, potentiates TNF-induced apoptosis through modulation of the nuclear factor-κB signaling pathway. Blood. 2007;110(10):3517-25.
17. Wang T, Wei J, Qian X, Ding Y, Yu L, Liu B. Gambogic acid, a potent inhibitor of survivin, reverses docetaxel resistance in gastric cancer cells. Cancer letters. 2008;262(2):214-22.
18. Chen B, Liang Y, Wu W, Cheng J, Xia G, Gao F, et al. Synergistic effect of magnetic nanoparticles of Fe3O4 with gambogic acid on apoptosis of K562 leukemia cells. International journal of nanomedicine. 2009;4:251.
19. Minami M, Nishio K, Ajioka Y, Kyushima H, Shigeki K, Kinjo K, et al. Identification of Curcuma plants and curcumin content level by DNA polymorphisms in the trnS-trnfM intergenic spacer in chloroplast DNA. Journal of natural medicines. 2009;63(1):75-9.
20. López□Lázaro M. Anticancer and carcinogenic properties of curcumin: considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. Molecular nutrition & food research. 2008;52(S1):S103-S27.
21. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. Biochemical pharmacology. 2008;75(4):787-809.
22. Ravindran J, Prasad S, Aggarwal BB. Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? The AAPS journal. 2009;11(3):495-510.
23. Aggarwal BB, Shishodia S, Takada Y, Banerjee S, Newman RA, Bueso-Ramos CE, et al. Curcumin suppresses the paclitaxel-induced nuclear factor-κB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. Clinical Cancer Research. 2005;11(20):7490-8.
24. Binion DG, Otterson MF, Rafiee P. Curcumin inhibits VEGF mediated angiogenesis in human intestinal microvascular endothelial cells through COX-2 and MAPK inhibition. Gut. 2008.
25. Hatcher H, Planalp R, Cho J, Torti F, Torti S. Curcumin: from ancient medicine to current clinical trials. Cellular and Molecular Life Sciences. 2008;65(11):1631-52.
26. Bayet-Robert M, Kwiatowski F, Leheurteur M, Gachon F, Planchat E, Abrial C, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. Cancer biology & therapy. 2010;9(1):8-14.
27. Ong E-S, Woo S-O, Yong Y-L. Pressurized liquid extraction of berberine and aristolochic acids in medicinal plants. Journal of Chromatography A. 2000;904(1):57-64.
28. Remppis A, Bea F, Greten HJ, Buttler A, Wang H, Zhou Q, et al. Rhizoma coptidis Inhibits LPS-Induced MCP-1/CCL2 Production in Murine Macrophages via an AP-1 and NFB-Dependent Pathway. Mediators of inflammation. 2010;2010.
29. Bhadra K, Kumar GS. Therapeutic potential of nucleic acid□binding isoquinoline alkaloids: Binding aspects and implications for drug design. Medicinal research reviews. 2011;31(6):821-62.
30. Qin Y, Pang JY, Chen WH, Zhao ZZ, Liu L, Jiang ZH. Inhibition of DNA topoisomerase I by natural and synthetic mono□and dimeric protoberberine alkaloids. Chemistry & biodiversity. 2007;4(3):481-7.
31. Tian X, Song Y, Dong H, Ye B. Interaction of anticancer herbal drug berberine with DNA immobilized on the glassy carbon electrode. Bioelectrochemistry. 2008;73(1):18-22.
32. Yadav KD. Cosmeceutical assets of ancient and contemporary ayurvedic astuteness. International Journal of Green Pharmacy (IJGP). 2016;9(4).
33. Chen H, Sun B, Pan S, Jiang H, Sun X. Dihydroartemisinin inhibits growth of pancreatic cancer cells in vitro and in vivo. Anti-cancer drugs. 2009;20(2):131-40.
34. Chen H-H, Zhou H-J, Wang W-Q, Wu G-D. Antimalarial dihydroartemisinin also inhibits angiogenesis. Cancer chemotherapy and pharmacology. 2004;53(5):423-32.
35. Zhou X-F, Ding Z-S, Liu N-B. Allium vegetables and risk of prostate cancer: evidence from 132,192 subjects. Asian Pacific Journal of Cancer Prevention. 2013;14(7):4131-4.
36. Buommino E, Baroni A, Canozo N, Petrazzuolo M, Nicoletti R, Vozza A, et al. Artemisinin reduces human melanoma cell migration by down-regulating αvβ3 integrin and reducing metalloproteinase 2 production. Investigational new drugs. 2009;27(5):412-8.
37. Chehl N, Chipitsyna G, Gong Q, Yeo CJ, Arafat HA. Anti-inflammatory effects of the Nigella sativa seed extract, thymoquinone, in pancreatic cancer cells. HPB. 2009;11(5):373-81.
38. Li C, Zhou L, Lin G, Zuo Z. Contents of major bioactive flavones in proprietary traditional Chinese medicine products and reference herb of Radix Scutellariae. Journal of Pharmaceutical and Biomedical Analysis. 2009;50(3):298-306.
39. Baumann S, Fas SC, Giaisi M, Müller WW, Merling A, Gülow K, et al. Wogonin preferentially kills malignant lymphocytes and suppresses T-cell tumor growth by inducing PLCγ1-and Ca2+-dependent apoptosis. Blood. 2008;111(4):2354-63.
40. Yang L, Zhang H-w, Hu R, Yang Y, Qi Q, Lu N, et al.

Wogonin induces G1 phase arrest through inhibiting Cdk4 and cyclin D1 concomitant with an elevation in p21Cip1 in human cervical carcinoma HeLa cells. Biochemistry and Cell Biology. 2009;87(6):933-42.
41. Lee J, Zhou H-J, Wu X-H. Dihydroartemisinin downregulates vascular endothelial growth factor expression and induces apoptosis in chronic myeloid leukemia K562 cells. Cancer chemotherapy and pharmacology. 2006;57(2):213-20.
42. Lee E, Enomoto R, Koshiba C, Hirano H. Inhibition of poglycoprotein by wogonin is involved with the potentiation of etoposide induced apoptosis in cancer cells. Annals of the New York Academy of Sciences. 2009;1171(1):132-6.
43. Enomoto R, Koshiba C, Suzuki C, Lee E. Wogonin potentiates the antitumor action of etoposide and ameliorates its adverse effects. Cancer chemotherapy and pharmacology. 2011;67(5):1063-72.
44. Shamim U, Hanif S, Ullah M, Azmi AS, Bhat SH, Hadi S. Plant polyphenols mobilize nuclear copper in human peripheral lymphocytes leading to oxidatively generated DNA breakage: implications for an anticancer mechanism. Free radical research. 2008;42(8):764-72.
45. Safarzadeh E, Shotorbani SS, Baradaran B. Herbal medicine as inducers of apoptosis in cancer treatment. Advanced pharmaceutical bulletin. 2014;4(Suppl 1):421.
46. Siriwatanametanon N, Fiebich BL, Efferth T, Prieto JM, Heinrich M. Traditionally used Thai medicinal plants: in vitro anti-inflammatory, anticancer and antioxidant activities. Journal of ethnopharmacology. 2010;130(2):196-207.
47. Wen L, Wu D, Jiang Y, Prasad KN, Lin S, Jiang G, et al. Identification of flavonoids in litchi (Litchi chinensis Sonn.) leaf and evaluation of anticancer activities. Journal of functional foods. 2014;6:555-63.
48. Thorpe Jr RJ, Wilson-Frederick SM, Bowie JV, Coa K, Clay OJ, LaVeist TA, et al. Health behaviors and all-cause mortality in African American men. American journal of men's health. 2013;7(4_suppl):8S-18S.
49. Steigerová J, Rárová L, Oklešťková J, Křížová K, Levková M, Šváchová M, et al. Mechanisms of natural brassinosteroid-induced apoptosis of prostate cancer cells. Food and chemical toxicology. 2012;50(11):4068-76.
50. Malíková J, Swaczynová J, Kolář Z, Strnad M. Anticancer and antiproliferative activity of natural brassinosteroids. Phytochemistry. 2008;69(2):418-26.
51. Liu T, Song Y, Chen H, Pan S, Sun X. Matrine inhibits proliferation and induces apoptosis of pancreatic cancer cells in vitro and in vivo. Biological and Pharmaceutical Bulletin. 2010;33(10):1740-5.
52. Kakarala M, Brenner DE, Korkaya H, Cheng C, Tazi K, Ginestier C, et al. Targeting breast stem cells with the cancer preventive compounds curcumin and piperine. Breast cancer research and treatment. 2010;122(3):777-85.
53. Freire-de-Lima L, Previato JO, Mendonça-Previato L. Glycosylation Changes in Cancer: an innovative Frontier at the interface of Cancer and Glycobiology. Frontiers in oncology. 2016;6:254.
54. Belický Š, Katrlík J, Tkáč J. Glycan and lectin biosensors. Essays in biochemistry. 2016;60(1):37-47.
55. de Oliveira Figueiroa E, Da Cunha C, Albuquerque P, De Paula RA, Aranda-Souza MA, Da Silva M, et al. Lectin-carbohydrate interactions: implications for the development of new anticancer agents. Curr Med Chem. 2017;24(34):3667-80.
56. Coelho LCBB, Silva PMdS, Lima VLdM, Pontual EV, Paiva PMG, Napoleão TH, et al. Lectins, interconnecting proteins with biotechnological/pharmacological and therapeutic applications. Evidence-Based Complementary and Alternative Medicine. 2017;2017.
57. Xu L, Cao J, Chen W. Structural characterization of a broccoli polysaccharide and evaluation of anti-cancer cell proliferation effects. Carbohydrate polymers. 2015;126:179-84.
58. Rao S, Hegde SK, Baliga-Rao MP, Palatty PL, George T, Baliga MS. An Aloe Vera-Based Cosmeceutical Cream Delays and Mitigates Ionizing Radiation-Induced Dermatitis in Head and Neck Cancer Patients Undergoing Curative Radiotherapy: A Clinical Study. Medicines. 2017;4(3):44.
59. Haniadka R, Kamble PS, Azmidha A, Mane PP, Geevarughese NM, Palatty PL, et al. Review on the use of Aloe vera (Aloe) in dermatology. Bioactive Dietary Factors and Plant Extracts in Dermatology: Springer; 2013. p. 125-33.
60. Kaul SC, Bhargava P, Wadhwa R. Ashwagandha for Cancer Metastasis: Bioactives and Basics of Their Function. Science of Ashwagandha: Preventive and Therapeutic Potentials: Springer; 2017. p. 243-62.
61. Mirjalili MH, Moyano E, Bonfill M, Cusido RM, Palazón J. Steroidal lactones from Withania somnifera, an ancient plant for novel medicine. Molecules. 2009;14(7):2373-93.
62. Wadhwa R, Singh R, Gao R, Shah N, Widodo N, Nakamoto T, et al. Water extract of Ashwagandha leaves has anticancer activity: identification of an active component and its mechanism of action. PLoS One. 2013;8(10):e77189.
63. Miethe C, Nix H, Martin R, Hernandez A, Price R. Silibinin Reduces the Impact of Obesity on Invasive Liver Cancer. Nutrition and cancer. 2017;69(8):1272-80.
64. Wilson DW, Nash P, Buttar HS, Griffiths K, Singh R, De Meester F, et al. The Role of Food Antioxidants, Benefits of Functional Foods, and Influence of Feeding Habits on the Health of the Older Person: An Overview. Antioxidants. 2017;6(4):81.
65. Esteghamati A, Mazaheri T, Rad MV, Noshad S. Complementary and alternative medicine for the treatment of obesity: a critical review. International journal of endocrinology and metabolism. 2015;13(2).
66. Johnson R, Bryant S, Huntley AL. Green tea and green tea catechin extracts: an overview of the clinical evidence. Maturitas. 2012;73(4):280-7.
67. Lima A, Oliveira J, Mota J, Ferreira RB. Proteins in soy might have a higher role in cancer prevention than

previously expected: soybean protein fractions are more effective MMP-9 inhibitors than non-protein fractions, even in cooked seeds. Nutrients. 2017;9(3):201.
68. Xu B, Chang SK. Comparative study on antiproliferation properties and cellular antioxidant activities of commonly consumed food legumes against nine human cancer cell lines. Food Chemistry. 2012;134(3):1287-96.
69. Lima A, Mota J, Monteiro S, Ferreira R. Legume seeds and colorectal cancer revisited: Protease inhibitors reduce MMP-9 activity and colon cancer cell migration. Food chemistry. 2016;197:30-8.
70. Wong BY, Nguyen DL, Lin T, Wong HH, Cavalcante A, Greenberg NM, et al. Chinese medicinal herb Scutellaria barbata modulates apoptosis and cell survival in murine and human prostate cancer cells and tumor development in TRAMP mice. European Journal of Cancer Prevention. 2009;18(4):331-41.