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Comprehensive Review

Can Using Plant Derived Agents for Cancer Like Geniposide and Genipin Change the Future of Cancer chemotherapy - A Short Communication

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Over centuries, plants have been exploited by mankind as sources of numerous cancer chemotherapeutic agents. Good examples of anticancer compounds of clinical significance today include the taxemes (like paclitaxel; taxol), vincristine, vinblastine and the podophyllum analogues which all trace their origin to higher plants. Although all these drugs along with different other options, gave some relief in cancer management, real breakthrough or cure has not been achieved With the research on the iridoid glycoside geniposide and its aglycone genipin, are being used right now as gold standard reference compounds in cancer studies. Here we highlight subtle points regarding effects on tumor development, cancer cell survival and death and mechanism of action. The biochemistry has been reviewed in ref on monoterpenes [1]. Most widely reported sources of geniposide are the fruits of Gardenia jasminoides Ellis (Rubiaceae), which was used traditionally in Chinese medicine. Many other species of this genus and other members from family Rubiaceae have been known to contain geniposide [2]. Hydrolysis product of geniposide, genipin is also found along with geniposide and several other derivatives like geniposidic acid. Geniposide on oral administration, gets converted to genipin in the intestine, that acts as the active principle. β-D-glucosidases of the intestinal bacteria were implicated in the transformation [3]. Further Kang., *et al*. showed that aglycone genipin is much more cytotoxicto human hepatoma HepG2 cells than geniposide [4] (figure 1).

Genipin and geniposide have been shown to be cytotoxic in various cancer cell types including colorectal cancer [5], pancreatic adenocarcinoma cells [6], AGS and SNU638 human gastric carcinoma cells [7], non small lung cancer H1299 cells [8], prostate (DU151, andPC3 cancer cells [9], HepG2, breast cancer (MDA-MB231cells, human leukaemia (K562, HL-60, U266, U937) cells [10] and tongue squamous carcinoma cells (HSC3). Although *in vivo* effect of compounds following oral administration might be variable based on the intestinal transformation, direct cytotoxicity or apoptosis induction are often > for aglycones than for their glycoside analogs. The reason why genipin and geniposide might not be considered lead compounds for anticancer treatment since effective dose of geniposide is much >100μM.

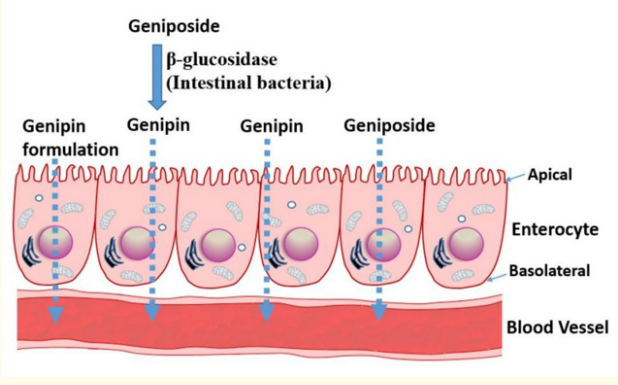

Figure 1

Effect on carcinogenesis

Doses as small as 5 and 10mg/kg of penta-acetyl geniposide has been shown to increase the latency of tumor development in animals. Topical application of geniposide on 12 O-tetracanoylphorbol-13-acetate (TFA)-induced promotion of skin tumors in mice, previously initiated with benzo [a] pyrine. When geniposide (0. 2

or 1.0µmol) was administered with TPA (15nmol) twice weekly for20weeks was reported to suppress tumor growth by 84% or 89%respectively. In same model geniposide further inhibited epidermal ornithine decarboxylase activity by TPA (5nM), along with skin inflammation and other markers of inflammation induced by TPA in mouth skin like H_2O_2. Further geniposide's effect on aflatoxin B1 (AFB1)-induced DNA-repair synthesis in primary cultured rat hepatocytes that were studied by Wang., *et al.* [11] showed geniposide suppressed AFB-induced DNA-repair synthesis via an increased AFB1 detoxication metabolism. Activities of antioxidants like GST, and GSH in AFB1 treated cultured cells thus increased by geniposide [12].

Effect on cancer metastases

Genipin suppressed the formation of intrahepatic metastases as well as tumour expansion in liver in an orthotopical implantation model at the non toxic concentration (60-120µg/ml) [12]. Cell motility and invasiveness via extracellular matrix (ECM)was also inhibited by genipin. Although expression of MMP2 was not affected, genipin upregulated TIMP2. Also genipins effect correlated with activation of p38 mitogen activated protein kinase (MAPK) signaling that correlated with apoptosis induction by genipin in cancer cells. Besides that multiple mechanisms of action take part in the anti metastaric action of geniposide/genipin and the crude extract preparation of plants that produce them (Figure 2).

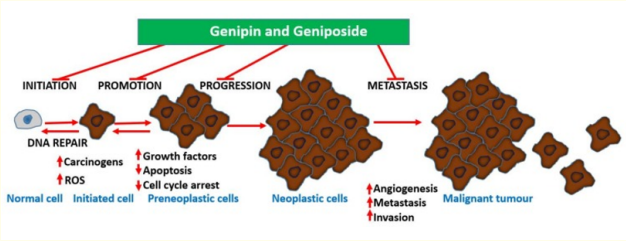

Figure 2

Lessons learnt

Mechanism correlated with cell cycle regulation

Apoptosis induction by anticancer agents is the common and rather gross mechanisms =>cellular morphology and biochemical alterations and death. Apoptosis induction and inhibition of cellular proliferation by geniposide and genipin have been shown to be coupled with cell cycle arrest [7]. E.g, G2/M phase arrest along with the induction of cyclin-dependent kinase inhibitor p21 (p21) and p21 dependent cyclins were shown to be induced by genipin in AGS human genetic cancer cells. As one expects, signaling pathways associated with this process are inevitably affected by genipin, and the transcription factor early growth respose (Egr1) p21cross-talk, among the mechanisms of apoptosis induction by genipin via caspase3 and a p53-independent mechanism in the Egr1-p21 signaling pathway. Overall induction of apoptosis by geniposide and genipin involved the activation of caspases that are known to mediate the common morphological, including DNA fragmentation, membrane blebbiing, and the formation of apoptotic bodies, that were widely reported along with cell death. Suppressing various functions of Bcl-2 predisposes cancer cells to increased apoptosis and cell death, as seen with different anticancer drugs.

General anti-inflammatory mechanisms

Common overlapping signaling cascades in carcinogenesis and inflammation is seen. On the basis of cancer-inflammation cross-talk, the anti-inflammatory effects of genipin and geniposide are via suppression of TNF-α production by genipin both *in vivo* and *in vitro*. The antioxidant effect of genipin and geniposide that correlates with their antidiabetic effect has been well shown [rev in 1] and includes the induction of antioxidant HO1and GSH via interaction of Nrf2. Through induction of HO1, genipin can also inhibit TNF-α induced vascular smooth muscle cell proliferation and migration.

Cancer cell killing by weaponizing oxygen

Under normal physiological conditions ROS get produced by a variety of mechanisms like induction of cytokines, under stress or inflammatory conditions. ROS regulate signal transduction in various cellular processes, that includes promoting cell proliferation at submicromolar or micromolar concentrations. Higher doses of ROS, induce apoptosis and further higher ones cause rapid cell death within minutes because of cell membrane death. Induction of apoptosis by genipin and geniposide through mitochondria dependent or independent pathways has been shown to be associated with the generation of ROS in various cancer cell lines. One of the link between ROS and induction of apoptosis is the stress activated protein kinase (SAPK) or JNK. When ROS get activated by drugs or other stimuli, including chemotherapeutic drugs, the activation of JNK is initiated => induction of apoptosis. Genipin induced apopto-

sis in Hep3B cells that was mediated by ROS/JNK activation of the mitochondrial pathway. JNK1/2 but not MEK ½ nor p38 MAPK was shown to be activated.

Emerging role of mitochondrian UCP2 in cancer biology and chemotherapy

Basic process of cellular respiration and oxidative phosphorylation in the mitochondria is based on the transport of protons (H+) out of the mitochondrial matrix to the intermediate space. The resulting mitochondrial membrane potential and protons electrogradient drives ATP synthase on reentry of protons. ATP generation in mitochondria is hence a result of coupling of the electron transport chain of ADP phosphorylation to form ATP. Located in the inner mitochondrial membrane, the UCP's also transport back into the mitochondrial matrix and thus abolish the proton gradient required for ATP production, but they also decrease O2- production. As cancer cells are under increased oxidative stress, they need an increased activity of UCP's for their survival. Based on this, regarding crucial role of UCP2 in cancer biology, the reported effects of genipin and analogs in this system appear to constitute a major anticancer mechanism of action. Although while inhibiting UCP2 could offer a therapeutic action in cancer cells, it could also be detrimental in some pathological conditions. E.g downregulation of UCP2 by genipin was shown to exacerbate diabetes induced kidney (proximal tubular cells) injury and apoptosis. Further genipin could also exacerbate palmitate induced hepatic steatosis via UCP2 ihhibition.

Drug potentiation

Through effect related to UCP2 inhibition, it was shown that drug resistant leukaemic cells could be sensitized to the cytotoxic action of menadione, doxorubicin and epirubicin when cotreated with genipin by Mailoux [13]. Crosstalk between UCP2 inhibition and the ROS/Akt. mechanistic target of rapamycin (mTOR)axis for genipin/everolimus anticancer synergism. Here mice xenografts of pancreatic adenocarcinoma and *in vitro* experiments, inhibition of UCP2 by genipin triggered the Akt/mTOR pathway by a ROS dependent mechanism. Tumor masses from mice injected with UCP2 (genipin) and mTOR (everolimus) revealed strong reduction in tumour volume and a number of mitosis, associated with a marked cytosolic glycolytic enzyme glyceraldehydes 3-phosphate dehydrogenase (GADPH) nuclear positivity. Thus genipin and everolimus could synergize in inhibiting cell proliferation both *in vivo* and *in vitro* through GADPH nuclear translocation. Thus the level of genipin/geniposide in terms of potency does not match that of taxanes or other mechanistic specific anticancer drugs, but their multiple mechanisms of action and chemical characteristics provide valuable lessons in advancing our knowledge in this field. These compounds have a plethora of effects in cancer development (carcinogenesis), survival, and metastasis i.e i)anticarcinogenic effect via antioxidant and anti-inflammatory (e. g. Nrf2, GPx induction) mechanismsii) targetingspecific enzymes (e.g GGT, MMPs)involved in carcinogenesis iii)Modulation of signal transduction pathways (e.g., MAPKsuch as JNK, p38, and ERK; PI3K, Akt, JAK1 etc)involved in cell proliferation, inflammation, and cell death iv)Suppression of production and function of proinflammatory cytokines (like IL-1, IL-6 and TNF-α)and other proteins (iNOS).V)Modulation of various transcription factors (Egr1, NF-kB, AP1, p21, STAT3)involved in inflammation and cancer biology and of transcriptional modulation like SMAD2 vi)Upregulation of genes /proteins that promote cell death and downregulation of survival genes/proteins; p53, Bcl2, Bcl-xL,, surviving, c-Myc, Bax, etc are classic e.g's vii)Enhancement of ROS formation both by NADPH oxidase and UCP2 pathway (fig4) viii)Triggering of cell cycle arrest (G1/S phase or G2/M phase by modulatingcyclin dependent kinasesix)Mechanisms related to topoisomerase 1poisoning for cytotoxicity and downregulation of P-glycoprotein that allow drug potentiation and /or combination therapy x)activation of procaspases (e.g procaspase-8 and 9)and caspasese including the final apoptosis executioner, caspase3.

Most crucial effect of genipin/geniposide appears to be linked to the double edged sword mechanism of life and death balancing act by ROS and or inflammation. They appear to enhance ROS generation via NADPH oxidase system and via the mitochondria primarily through a UCP2 mechanism in cancer cells. The effect especially by genipin, suggests their use as gold standard reference compounds in cancer pharmacology studies. The same mechanism involved in carcinogenesis is also targeted by genipin/geniposide as evidenced from both *in vitro* and *in vivo* data. Such an effect perhaps obtainable even at smaller doses, appears to have a relevant value for therapeutic approaches focused on the chemoprevention or nutraceutical utilization of plant resources. In this connection, the common fruits of the plants yielding genipin/geniposide are important resources to be taken into consideration. The demise of genipin/geniposide as anticancer agents appear to

lie on their dual pro-oxidant/antioxidant effect, with their overall anticancer effect on established cancers appearing to be mediated at fairly large ones. Thus future studies are needed to disentangle these conflicting pharmaco logical properties, supposedly through structural design, to confer these compounds a far >potency. In the meantime, the lessons that we have learnt from these compounds as anticancer agents, from their pharmacokinetic profiles to their mechanism s of action, are further examples of the role played by plants as valuable sources of anticancer drugs.

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