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Multi Hit Phyto Therapeutic Strategy- A Cancer Cure Concept

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Abstract

Cancer being a multistep, and multi profile disease of multiple etiology, the complete cure for this emperor disease is out of reach in clinical oncology, in spite of multifarious drugs and innovative modalities of treatment procedures. Even the most successful chemotherapy is unable to cure the stage 3&4 cancer wherein the cancer cells take up the metastatic profile and migrate to keep away from the primary site to distant organs and settle by immune- compromisation to seed and breed the secondary population of cancer cells which differ from their primary progenitor cells in various aspects.

Metastatic cancers until this hour remain as incurable especially in breast cancer patients with currently available therapies. Research investigation using cell lines and clinical studies are hectically striving to find cures for such IIIrd and IVth slater stage cancers or resistant cancers permanently and to prevent the disease relapse. The perusal of the results of some case studies in women revealed that both surgical ablation and chemotherapeutic intervention proved futile and instead of palliating the patient's health condition, they drove the patients to fatal ending due to aggressive invasion of metastatic cells consequent to invasive surgery from the primary site to such vital organs as brain, lung and liver and the consequent collapse.

Keywords: Chemotherapy; Clinical studies; Metastatsis

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When a review about the invasive metastatic cancer cells is made, several things become obvious. The resistant cancer cells and cancer stem cells have no "SWITCH OFF" mechanisms and do not undergo apoptosis, not killed by the free radicals, become radiation cum chemo resistant, express entirely new antigenic profiles over their surface, show more tendency towards invasion, make immune compromising with peripheral organs, evade the hosts immune surveillance and their stem cells characteristics enable their non-stop proliferation, employ the various anti-apoptotic pathways for their survival etc., Hence even the ultra modern chemotherapeutic drugs as well as hormonal adjuvant therapy failed to contain the relapse of metastatic cancer cells and prevent the death of the patients.

Primary cancer cell metastatic and secondary niches revealed that the metastasizing cancer cells though have the unlimited genomic potential to undergo proliferation, their energy potential for their continuous divisions and DNA replications are very much limited within and require the supply of constituents mainly glucose from the without. In view of the above contention, the failure of chemotherapeutic drugs to contain the secondary population of malignant cells could be attributed to their untiring and unwearied conditions in vivo due to unstinted supply of their vital nutrients in the form of glucose and their mechanism of pentose shunt and other modes of glucose derivation such as the enhanced alkaline phosphatase activity etc.

So until this time, existing therapeutic treatments are not able to eradicate these metastatic cancers, the cure for cancer in this context and situation lies not in pumping more drugs inside the body of the patient, who is immunologically nude and bereft of any immunological defense mechanisms against the cancer cells armamentarium. Here the question still remains as an enigma viz., whether the immune depression is either a precedent decree or an aftermath of cancer. It is like the chicken and egg dilemma.

In chemotherapy, drugs are targeting the cancer cells in specific stage and accordingly they are designated as S phase specific; M phase specific and cycle none phase specific drugs. In the growth kinetics of cancer cells, the abundance of cell population may be expected in their log phase by any one type of drugs mentioned per se, but targeting the cancer cells at its exponential growth phase may kill only partially the cells of the total population. Hence the residual cells in different inter phases will restart their division potential.

Unlike the bacterial cell population which show uniform growth kinetics, the cancer cells or the cell groups are kaleidoscopic in nature and each group has its own growth kinetic cues, which is determined by various intricacies of both intrinsic and extrinsic factors. The main determinants of their division potential and growth kinetics are the supply or input of glucose substrate, warburg's effect and the consequent formation/production of lactic acid, the trigger of COX-2 enzymes activity to generate the prostaglandins-E, the growth promoters of cells, and also the production of pro inflammatory cytokines and other protein aceous and fatty factors etc.,

Adjuvant chemotherapy combined with radiation and surgery has resulted in complete remission only in immuno competent patients and fails to do so in immune incompetent patients. As long as the chemotherapy drugs are individualistic in mechanism of action and function like "Single stitch common for all" only differential results of recovery from disease may be expected and complete cure 100% needs immune competency.

The basic concept of magic bullet in chemotherapy could not be realized and any number of drugs with uni model mechanism of action which cytotoxically kill the cancer cells through oxidative stress by free

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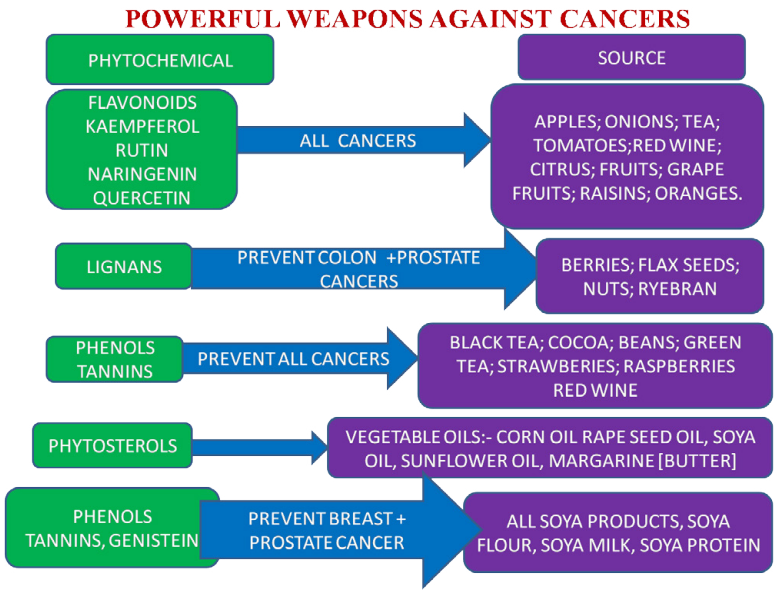

Figure 1: Investigations of herbal secondary metabolites on various cancers.

radicals generation cannot be called in the true sense "Magic bullets" but only as tragic bullets" [1-3].

Chemotherapy should have to go a long way in targeting the cancer cells, by circumventing the formidable obstacles which the cancer cells employ and continue to promote their survival.

The residual cancer cells besides recapitulating the embryonic gene's functional attributes of de differentiation, they may also behave like prokaryotic bacterial cells which have evolved mechanisms to overcome the free radicals injury by synthesizing defensive protein/ enzymes to eliminate them. The bacterial general stress response proteins play the role of molecular chaperones to prevent protein aggregation and refolding to enable the bacterial cell survival. Similar atavistic mechanism may not be unexpected and it may be of paramount importance in view of the evolutionary descent of cell lineage in eukaryotes cancer cells [4].

The cyto toxic killing of cancer cells of all categories require novel mechanisms of "Multi Hit" and "Multi Injuries" surpassing every cancer cell mechanism viz.,

- Expression of Tumour surface specific Receptors.
- Receptor binding to hormones.
- Cytoplasmic protein factors.
- Mitochondrial mechanism of anti apoptosis.
- Transcription and synthesis of cell survival proteins (enzyme).
- Synthesis of growth promoting prostaglandins through COX-2 activity.
- Glutathione protection and various cell signalling pathways.
- Extracellular matrix composition.
- Matrix degrading enzymes (MMPs).
- Obtaining the supply of glucose, the main energy metabolite of cancer cells.
- Gluconeogenesis process of cancer cell metabolism.
- Neoangiogenesis.
- Host immunosuppression.

Though chemotherapeutic drugs could bring cytotoxic death of cancer cells by attacking some of the above mentioned functionalities, they are invariably beset with innumerable side effects which are inevitable and cannot be overcome in immuno incompetent patients, ultimately driving to palliative dead end therapy. Towards this, recent investigations on herbal secondary metabolites revealed the expected outcome of cancer cells death. The various phytochemicals viz, Polyphenols, Flavonoids, Saponins, Triterpenes, Alkaloids, β-Carotenes etc. have brought the above results in studies as shown in Figure 1. The "Multi Hits" or "Multi Injuries" mechanism of the above secondary metabolites show parallelism to chemotherapeutic drugs in studies and may be expected to do the same in vivo but without side effects unlike the chemotherapy. These molecules could give ample evidence and answer to the question "where the hook lies to angle the cancer cells growth and proliferation".

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