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Hypothesis of a Holistic Treatment of Cancer: Crab Method

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Abstract**—**The main hindrance to total cure of cancer is a) the failure to control continued production of cancer cells, b) its sustenance and c) its metastasis. This review study has tried to address this issue of total cancer cure in a more innovative way. A 10-pronged "CRAB METHOD", a novel holistic scientific approach of Cancer treatment has been hypothesized in this paper. Apart from available Chemotherapy, Radiotherapy and Oncosurgery, (which shall not be discussed here), seven other points of interference and treatment has been suggested, i.e. 1. Efficient stress management. 2. Dampening of ATF3 expression. 3. Selective inhibition of Platelet Activity. 4. Modulation of serotonin production, metabolism and 5HT receptor antagonism. 5. Auxin, its anti-proliferative potential and its modulation. 6. Melatonin supplementation because of its oncostatic properties. 7. HDAC Inhibitors especially valproic acid use due to its apoptotic role in many cancers. If all the above stated seven steps are thoroughly taken care of at the time of initial diagnosis of cancer along with the available treatment modalities of Chemotherapy, Radiotherapy and Oncosurgery, then perhaps, the morbidity and mortality rate of cancer may be greatly reduced.

Keywords**—**ATF3 dampening, auxin modulation, cancer, platelet activation, serotonin, stress, valproic acid.

I. Introduction

THIS review study has hypothesized a holistic 10 pronged "Crab Method" of treatment of cancer. It has tried to take into consideration the three main factors for failure of Cancer treatment, namely a) continued production of malignant cells, b) the ability of malignant cells to sustain for prolonged periods and c) distant spread of cancer cells.

With the intention of improving the mortality and morbidity of the dreaded disease, Cancer (Latin word for Crab having 10 legs), seven different points of interference has been suggested (other than available Chemotherapy, Radiotherapy and Oncosurgery). They are namely: 1) Mental Stress, 2) ATF3 gene, 3) Platelet Activation, 4) Serotonin, 5) Auxin, 6) Melatonin, and 7) HDAC Inhibitors. The causal relation with cancer of these above factors and the probable mode of interference is the main focus of this study.

A. Stress and Cancer

Recent studies have found a strong association of both 'obesity' and 'mental stress' with the increasing incidence of cancers at various sites and their adverse effects on the morbidity and mortality [1], [2].

When mice were fed on high fat diet to induce obesity, there was a marked increase in the progression of melanoma [3].

Another mouse model study has found that stress induced β-adrenergic activation increased macrophage infiltration into primary tumor cells, thereby inducing pro-metastatic gene expression in primary breast cancer. This has led to 30-fold increase in metastasis to distant tissues. Treatment with β-antagonist drugs has been effective in inhibiting metastasis. Moreover, inhibition of macrophage infiltration by Colony stimulating factor receptor (CSF-1R) inhibitor, GW2580, has also been found to be effective in retarding secondary spread [4].

B. ATF3 and Cancer

Amongst the mammalian ATF/CREB family of transcription factors in the macrophages, Activating Transcription Factor 3 (ATF3) is a transcriptional repressor involved in cellular responses to extracellular signals [5], [6].

The mRNA level of ATF3 gene is greatly increased when the cells are exposed to stress signals, both in animal experiments, and in cultured cells [7], including many of those encountered by cancer cells (tumor microenvironment) e.g. Prostate carcinoma, Breast carcinoma, Hodgkin lymphoma [8].

ATF3 then regulates the expression of a variety of genes, in inflammation (mediated by immunoglobulin & immune complexes) which has got a significant role to play in cancer development and progression [9]-[12].

A recent study has found that ATF3 gene expressed in non-cancer host stromal mononuclear cells, but not cancer epithelial cells, leads to worst outcome and may act as an independent predictor for breast cancer death thereby signifying the importance of host stress response. Supporting data from mouse models has shown less efficient breast cancer metastasis in Atf3-deficient mice than in WT (Atf3+/+) mice. So, dampening ATF3 expression in the host may be a potential therapeutic approach [13].

Chemotherapeutic drugs presently in use have strangely both anti-cancer properties and a pro cancer effect by increasing chemo-resistance and cancer metastasis [17]. The chemotherapeutic agents which also acts as stressors, including Paclitaxel [PTX] [14], cisplatin [15], and doxorubicin [16] induces ATF3 gene in the tumor microenvironment (non-cancer host cells) which in turn plays an important role in producing this paradoxical effect.

Actually, the cellular stress response which evolved to promote tissue repair, has preferred to help cancer cell survival and progression [18], [19].

As the ability of PTX to exacerbate metastasis was completely abolished in ATF3 deficiency in host, rationally

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ATF3 dampening may improve the efficacy of chemotherapy.

C. Platelet Activation

Platelet activity is initiated and increased by physical, and more so by emotional stress, as well as stress-related psychiatric or somatic disorders. This is mediated by the activating properties of epinephrine and nor-epinephrine on the platelet.

There are increased levels of platelet 5 HT in paranoid schizophrenia and increased platelet 5-HT-2A receptor density in depression [20]-[29].

The activation of platelets is followed by platelet bridging and platelet aggregation with the binding of fibrinogen to its major receptor, active form of glycoprotein receptor GPIIb/IIIa [25]. The activated platelets also adhere to Lymphocytes mainly via platelet P-selectin and lymphocyte P-selectin glycoprotein ligand-1 (PSGL-1) and sialyl saccharides, thus forming platelet-leukocyte aggregates, PLAs. Therefore, PLAs are suggested to be a very sensitive marker of platelet activation in vivo [30]-[32]. A study on the correlation of PLA and acute mental stress showed peak level at 30 min, returning to base level at 75 min [33], [34].

Activated platelets have quite a significant role in both

a) Tumor angiogenesis
b) Tumor metastasis.

1. Tumor Angiogenesis Role

Activated platelets can secrete pro-angiogenic growth factors like platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), protease like MMP9; phospholipids and other microparticles to promote angiogenesis. Activated platelets can also directly bind to Endothelial cells (EC) to support angiogenesis [35], [36]. The platelet activation and coagulation product fibrin, commonly exist in tumors, along which ECs can survive and migrate to form new blood vessels.

Activated platelets can recruit bone marrow-derived cells to the site of neovascularization by secretion from α-granules, which suggests a role of platelets as communicators between hypoxic tissue and the bone marrow [37]. Platelet derived factors support tumor angiogenesis by protecting the integrity of the angiogenic and inflamed tumor vessels. [36], [38], [39].

Tumor cells secrete a Vascular permeability factor (VPF), which shows a significant homology with PDGF and VEGF.VPF has been found contribute to tumor angiogenesis. Moreover VPF also induces an increase of von Willebrand factor (vWF) which initiates platelet aggregation [40].

2. Tumor Metastasis Role

Tumor cells with platelet activation capacity can form more metastasis in mice with xenografted tumors [41]. Metastasis was reduced grossly in cases of thrombocytopenia in several mouse models [42], [43].

Below three mechanisms for the metastasis supporting role of platelets are described.

1. Tumor cells are protected from shear stress and immune cell attack in the blood circulation by the platelets after intravasation by acting as a physical guard to help them escape immune elimination [44]. Platelets may also inhibit Natural Killer (NK) cell cytotoxicity via platelet-derived Transforming growth factor beta TGF-β [45] or other secreted factors released upon activation [46].
2. Activated platelets encourage tumor cells to roll and tether on the vessel wall, which are necessary for the extravasation. Selectins on the platelet surface could promote tumor cell (expressing selectin ligands) adherence to the endothelium transiently [47]. Moreover, the beta3 integrin-mediated binding to activated platelets is an efficient mechanism for melanoma cell arrest under flow, and this may contribute to the role of platelets in metastasis [48].
3. Platelet secretes prometastatic factors and matrix degrading enzymes to facilitate metastasis. From the α-granules of the platelets, VEGF-A, Epidermal growth factor (EGF), PDGF and TGF-β and serotonin and histamine from dense granules of the platelets are released which affect the vascular permeability and enhance metastasis [49].

Direct contact of the tumor cells with platelets together with Platelet-derived TGF-β; activate the TGF-β/Smad and nuclear factor-κB (NF-κB) pathways in cancer cells, resulting in their transition to an invasive mesenchymal-like phenotype and increased metastasis in vivo. Ablation of TGFβ1 expression solely in platelets and inhibition of NF-κB signaling in cancer cells protects against lung metastasis in vivo [50].

In tumor cells, NF-κB is active either due to mutations in genes encoding the NF-κB transcription factors themselves or in genes that control NF-κB activity (such as IκB genes); in addition, some tumor cells secrete factors that cause NF-κB to become active.

Blocking NF-κB can cause tumor cells to stop proliferating, to die, or to become more sensitive to the action of anti-tumor agents. Thus, NF-κB is a target for anti-cancer therapy [51]. Disulfiram, olmesartan and dithiocarbamates can NF-κB signaling cascade [52].

LPA & MMP

Recently, the importance of platelets in the progression of malignant tumors has been studied [53], [54]. LPA (lysophosphatidic acid), which is a simple lipid with mitogenic properties is rapidly released by activated platelets [55], [56]. Moreover, LPA has been found to be useful as a diagnostic and prognostic biomarker of ovarian cancer [57]. In the initiation and progression of several cancers, such as colon, ovarian, prostate, breast, melanoma and thyroid, LPA is involved [58], [59]. The effects of LPA are mediated by at least six different G protein-coupled receptors [LPA1-6] [60]. Selective blockage of LPA1 inhibits cancer cell proliferation and invasion. [61]-[63]. The activity of matrix metalloproteinases, MMP2, MMP7 and MMP9 in cancer cells are up regulated by LPA [64]-[67].

The MMPs are enzymes that have role in cancer progression. MMPs especially MMP-9, have a critical role in certain aspects of tumor metastasis such as tumor-induced angiogenesis, tumor invasion, and establishment of metastatic

foci at the secondary site [68], [69]. A study in a mouse model has shown that induced thrombocytopenia leads to destabilization of tumor vessels with intratumoral hemorrhage, thereby reducing tumor cell proliferation and increased necrosis [70].

Recent studies have shown that in cancer patients, selective inhibition of platelet activity by low molecular weight heparins (LMWHs) not only reduces risk of embolism, but also effectively inhibits metastasis by suppression of angiogenesis and thus improving their survival rates [71]-[74]. So, the process of platelet activation may be tried as a therapeutic intervention. Lung metastasis and inhibition of TCIPA (tumor cell-induced platelet aggregation) can be greatly reduced by the oral GPIIb/IIIa antagonist, XV454, in a mouse model [75].

D.Serotonin and Cancer

Psychological stress in conscious rats had been found to markedly increase the levels of extracellular 5-HT levels in basolateral amygdaloid nucleus and the prefrontal cortex due to activation of serotonergic neurons in these brain regions [76]. This study also suggests that there is a relationship between anxiety and 5-HT release in the prefrontal cortex [77].

An overview of 30 years of research on stress and 5-HT, indeed favors the hypothesis that numerous components of central serotonergic systems are sensitive to stressors [78]. Numerous stressors increase 5-HT synthesis/ turnover [79].

A recent study demonstrates that FOXO3a functions as a growth factor in serum-deprived HCC (Hepatocellular carcinoma) cells and serotonin promotes the proliferation of serum-deprived HCC cells via up-regulation of FOXO3a, in the presence of sufficient levels of the serotonin receptor 5-HT_{2B}R. Therefore, drugs targeting the serotonin-5-HT_{2B}R-FOXO3a pathway may provide a novel target for anticancer therapy [80].

Another study provides evidence that serotonin is involved in tumor growth of hepatocellular cancer by activating downstream targets of mTOR, and therefore, serotonin-related pathways might represent a new treatment strategy [81].

In hormone refractory PC3 prostate cancer cells, 5-HT1A and to a greater extent 5-HT1B antagonists significantly inhibit growth and induce apoptosis. This effect is most likely mediated via 5-HT1A and 1B receptors. Therefore, the results imply that 5-HT1A and 5-HT1B receptor antagonists may act as potential antineoplastic agents [82].

A study addresses the role of 5-HT in Erk1/2 and Akt activation in prostate cancer cells, which proves towards neuroendocrine factors facilitating progression and migration of prostatic cancer cells in an androgen-deficient environment. The action of 5-HT was inhibited to varying degrees by inhibitors of MAPK and PI3K, as well as by a 5-HT receptor subtype 1A antagonist. The data presented in that study also identifies 5-HT receptors as a novel target in castration-resistant PC [83].

The proliferative effect of serotonin on cholangiocarcinoma growth and the inhibition of serotonin production effectively inhibits tumor growth has been shown in a recent study. Furthermore, it has also been found that inhibition of the serotonin receptors 5HTR 1A, 5HTR 2A, 5HTR 2B, 5HTR 4 and 5HTR 6 effectively blocked the growth promoting effects of serotonin.

The major findings of one study relate to the dysregulation of serotonin metabolism in cholangiocarcinoma. A few significant findings in that study are as follows:

a) Expression of the enzyme responsible for serotonin synthesis in the gastrointestinal tract, TPH1, is up regulated in cholangiocarcinoma;
b) The enzyme responsible for serotonin degradation, MAO A, is markedly decreased in cholangiocarcinoma samples;
c) That this results in an overall increase in serotonin secretion from cholangiocarcinoma cells and in the bile from cholangiocarcinoma patients.

Therefore, agents that suppress serotonin production may be very much useful in the treatment of cholangiocarcinoma [84].

Serotonin has an important role in tumor growth, especially colon cancer, by regulating angiogenesis by reducing the expression of matrix metalloproteinase 12 (MMP-12) in tumor-infiltrating macrophages. This leads to lower levels of 'angiostatin' which is an endogenous inhibitor of angiogenesis. Hence, serotonin might represent a novel target for the prevention and treatment of colon cancer [85].

MMP-12 cleaves plasminogen into angiostatin, which suppresses angiogenesis in solid tumors. Enhanced transcription and activation of MMP-12 observed in tumors of serotonin-deficient mice entailed higher levels of circulating angiostatin, causing a reduction of tumor vascularity, enhanced hypoxia, and consequently, tumor necrosis [86], [87]. Serotonin-dependent effects were reproducible in Lewis lung cancer, in accordance with previous studies showing supra-normal serotonin levels to enhance lung cancer proliferation [88], [89] and macrophage-derived MMP-12 to regulate Lewis lung cancer growth [86], [87].

E. Auxin and Cancer

Auxins (Indole-3-acetic acid), a plant hormone essential for plant body growth and development interacts with its receptor TIR1 (Transport inhibition response 1), which is similar to human ubiquitin ligase enzymes (SKP2). Auxin helps TIR1 to bind to its peptide substrate tightly thus may have an important role to play in human cancer because many types of cancer are caused by dysregulation of ubiquitination (the first breast cancer susceptibility gene Brca1 is a ubiquitin ligase) [91], [92]. Also serotonin in plants which regulates root development acts as a natural auxin inhibitor [90]

Either blocked degradation of oncogenic proteins/ growth-enhancing factors or accelerated degradation of growth-suppressing proteins may disrupt the pathways controlling cell cycle progression, cell death, or survival, leading to cancer development [93], [94]

Ubiquitination and the ubiquitin-mediated proteolysis play an important role in tumorigenesis and cell growth. A powerful approach for cancer treatment would be to target the components involved in these processes. The first proteasome

inhibitor for clinical use in human cancers is Bortezomib [95].

The F-box protein SKP2 (S-phase kinase-associated protein 2) forms a complex with CUL1, SKP1, and a RING finger protein RBX1, together termed SCF^{SKP2} [96]. Several important cell cycle regulators, including $p27^{KIP1}$ and $p21^{CIP1}$ undergo ubiquitination by SKP2 [97]-[99]. SKP2 also plays a critical role in EGFR-mediated AKT ubiquitination and membrane recruitment [100].

The oncogenic potential of SKP2 was suggested by its over expression in a variety of human cancers [101], [102]; importantly, this over expression of SKP2 showed an inverse relationship with p27KIP1 [103], [104]. The protein levels of SKP2 could indicate the prognosis, inversely proportional to survival rate of patients [100], [103], [105].

Given the importance of SKP2 in regulating degradation of tumour suppressors and its clear oncogenic potential, inhibiting SKP2 may represent a unique opportunity for the treatment of different types of tumours.

A study focused on Auxin alone and its antiproliferative potential, with emphasis on modulation of the cell cycle, of natural (IAA) and synthetic (2,4-D) Auxin, showed cytostatic effects on selected human tumor cell lines, induce strong G1 arrest, along with a drastic decrease in the percentage of S-phase cells in MCF-7 cell line. This phenomenon demonstrates that Auxins may have novel, unexploited antitumor potential [106].

F. Melatonin and Cancer

Melatonin, (N-acetyl-5-methoxytryptamine) is an indole amine secreted by the pineal gland, is an oncostatic agent. It has got antioxidative [107]-[112], anti-inflammatory and anti-tumor activities [113]-[120]. It also has the capability of modulating several signal transduction pathways associated with cell survival, proliferation, apoptosis and invasion [121]-[125].

Additionally, melatonin inhibits the growth of a variety of cancers: lung [126]-[128], breast [129]-[133] prostate [134]-[137], liver [138], [139], colon [140], [141].

Anti-cancer property of melatonin is related to its different qualities e.g. anti-proliferation [126], induction of apoptosis [126]-[128] inhibition of invasion and metastasis [142], [143], anti-angiogenesis [129], [144], and enhancement of immune modulation [145], regulation of the estrogen receptor expression and trans-activation, modulation of the enzymes involved in the local synthesis of estrogens [166]. Melatonin increases the efficacy and reduces the side effects of both radio-therapy and chemotherapy [146], [147].

Melatonin, through increasing adhesion by elevating E-cadherin and β1-integrin expression or modulating microfilament, can inhibit tumor invasion [148]-[150], and decreasing matrix metalloproteinases (MMPs) production [151].

The effect of melatonin on the migration of human lung adenocarcinoma A549 cells was observed and it was found that there is an association between JNK/MAPK [c-jun-N-terminal kinases (JNK)/ mitogen activated protein kinase (MAPK)], pathway and the expression of tight junction (TJ) related proteins occluding, myosin light-chain kinase (MLCK), osteopontin (OPN). The melatonin may inhibit A549 cell proliferation and play an important role in the inhibition of tumor progression [152].

Melatonin has been found to have a synergistic effect along with Cisplatin in human cervical cancer cells [153], in high concentrations has a pro-apoptotic effect on pancreatic carcinoma cells [154], [161], renal cancer cells [155], [160] and in the treatment of neuroblastoma [156]. It has also anti cancer effects on gastro intestinal cancer [157], in breast cancer [163]. Melatonin, though inhibits apoptotic processes in normal cells, modulates autophagy and activates the intrinsic and/ or the extrinsic apoptotic pathway in cancer cells [164] and is helpful even in tumor models unresponsive to melatonin alone, by amplifying significantly the cytostatic and the cytotoxic effects of other conventional anti cancer drugs [158], [159], [162], [165], [167].

A recent study demonstrated that melatonin supplementation down-regulated, Proliferating-cell nuclear antigen (PCNA) which is a molecular marker for proliferation and reduced the viability in both lung cancer A549 and PC9 cells [127]. Melatonin as a co-treatment with conventional cancer therapies would improve the wellbeing of the patients [168].

Besides these oncostatic properties, melatonin deserves to be considered in the treatment of cancer (doses in the 100 – 500 mg/day range) for two other reasons. First, because its hypnotic-chronobiotic properties, melatonin can effectively be used for sleep disturbances, a major co-morbidity in cancer. Second, because melatonin's anxiolytic and antidepressant effects, it has a possible application in two other major co-morbidities seen in cancer patients, i.e. depression and anxiety [169].

Melatonin acts as a proteasome inhibitor [160], which has an anti-proliferative action on human breast cancer cells. Melatonin specifically inhibits estrogen induced transcription mediated by ERα (estrogen receptor alpha) at the ERE (estrogen responsive element) and AP1 (Activator protein 1) gene promoters [92].

G.HDAC Inhibitors Specially Valproic Acid and Cancer

Acetylation of Histones plays a key role in epigenetic regulation of gene expression in carcinogenesis. Histone deacetylases (HDAC) inhibitors induce cancer cell cycle arrest, differentiation and cell death, reduce angiogenesis and modulate immune response, and so may be used as an anti-cancer drug in combination with other anti-cancer drugs and/ or radiotherapy.

HDAC inhibitors have been approved; Vorinostat for cutaneous T-cell lymphoma (CTCL), Belinostat for peripheral T cell lymphoma (PTCL)), and Panobinostat for therapy of multiple myeloma [170].

The anticancer effects of HDAC inhibitors are different and depend on a type of cancer and dose used e.g. Valproic acid (VPA) inhibit the invasiveness in bladder cancer [171].

Mechanisms:

a) HDAC inhibitors induces cell cycle arrest by the increased expression of cell cycle genes such as CDKN1A (Cyclin dependent kinase inhibitor p21) [172]-[174].
b) Apoptosis in tumor cells is induced by the HDAC inhibitors by regulation of pro-apoptotic and anti-apoptotic genes [175]-[177]. The mechanisms include activation of both extrinsic and intrinsic apoptotic pathways.
c) Autophagy induction in apoptosis-resistant cancer cells is an important feature of HDACI. It works through several signaling pathways e.g. downregulation of AKT-mTOR signaling [178], VPA in prostate cancer cells [179].
d) Anti-cancer effect of HDACI, is also due to its capability to alter long non-coding RNA (IncRNA) expression e.g. abexinostat in breast cancer cells [180].
e) Activation of some of protein kinases i.e. ERK (which modulate biological processes like cell growth, differentiation and apoptosis) is done by the HDACI [181].
f) Anti angiogenic effect of VPA is done by enhancing production of the anti-angiogenic proteins thrombospondin-1 and activin A via downregulation of pro-angiogenic factors such as the basic fibroblast growth factor (bFGF) [182].
g) HDACI induces modulation of immune response and enhances the functions of NK cells and CD8 T cells [183].

VPA inhibits the growth of pancreatic and colon, and oral squamous cell cancer cell growth by down-regulation of β-amyloid precursor protein (APP) [184].

VPA when administered even in lower doses to prostate cancer reduces the net proliferation rate both in androgen receptor-positive and androgen receptor-negative prostate cancer cells. This is due to the increased caspase-2 and caspase-3 activation [185]. Moreover, chronic VPA treatment results in statistically significant reduction of tumor growth and volume in vivo. This enhanced activity results from capturing the resistant quiescent cells.

It is therefore concluded that acute treatment has nominal effects on prostate cancer cell survival and proliferation, but chronic VPA results in profound decreases in proliferation, independently of androgen regulation [185]

Monoamine oxidases (MAOs) A and B are mitochondrial isoenzymes which catalyze the oxidative deamination of dietary amines and monoamine neurotransmitters, such as serotonin, norepinephrine, dopamine. Dysfunction of MAO A leads to abnormal levels of these neurotransmitters resulting in many psychiatric disorders including severe aggression/anti-social behavior [186], [187]. VPA often used as a mood stabilizer/in epilepsy, exerts its effect is through regulating the brain levels of serotonin. VPA activates monoamine oxidase (MAO) A catalytic activity via Akt/FoxO1 signaling pathway that degrades a number of monoamine neurotransmitters, including serotonin [188]. Therefore, VPA also acts as an anti-cancer agent through the serotonin pathway.

II. Conclusion

Apart from the available chemotherapy, radiotherapy and surgery, the following seven steps have been suggested in this review study, if taken care of, may perhaps help to reduce the morbidity and mortality of a dreaded disease, cancer.

1. Estimation of Platelet 5HT level which is a Stress marker. Treatment of Mental Stress with medicine [189].
2. ATF3 dampening in the host may be tried as a potential therapeutic approach.
3. a) PLA to be measured routinely in cancer patients.
b) NF-κB inhibitors may be used selectively as anti-cancer therapy e.g. Disulfiram, olmesartan etc.
c) Selective blockage of LPA_1 and LPA_2 may be tried.
4. i) Drugs targeting the serotonin-5-HT_{2B}R-FOXO3a pathway and normalising 5HT level to be used.
ii) Agents that modulate the metabolism of serotonin may be useful for cancer treatment.
iii) 5-HT1A, 5-HT1B, 5HTR 2A 5HTR 2B, 5HTR 4 and 5HTR 6 effectively blocked the growth promoting effects of serotonin and selective blocking of these receptors may act as potential antineoplastic agents.
5. Inhibiting SKP2 may be tried for the treatment of different types of tumors.
6. Melatonin level to be measured routinely in cancer patients. Melatonin supplementation, due to its oncostatic properties, will immensely add on to the improvements with conventional cancer treatment.
7. Chronic VPA administration may result in profound decreases in proliferation in cancer. Different HDACI have been approved as anti-cancer agents.

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