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Paradoxical Role of Urinary Extracts in Tumour Regression or Progression-A Critical Overview

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Review Article

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ABSTRACT

The massive current literature on cancer has inadvertently failed to sufficiently emphasize on the innate biological regulators of tumour growth. The attempts to understand the normal control of tissue growth and its derangement in cancer, however, may hold the key to the entire problem of neoplasia. Ewing has stated that the problem of cancer might well be considered as a disturbance of the growth energy of a body tissue. Albert Szent-Gyorgyi, more metaphorically, stated about the control of cancer cell proliferation and its spread, "The problem is not what makes the cell divide, but what has gone wrong with the mechanism so that it cannot stop; a cancer cell is comparable to a car on a slope. If it starts running, the question is not what makes it go, but what's wrong with the brake?" The purpose of this review is to summarize and examine the relevant literature that has addressed the role of urine extracts in regulating tumour progression and regression.

INTRODUCTION

The history of the use of urine extract in regulating tumour growth in the western literature goes back 1930's. In 1934, Bischoff and Maxwell in their studies on the role of hormones in cancer reported a tumour resistance factor in normal urine that affect carcinoma. They identified what they called as a tumour-depressor factor that was difficult to dissolve in ethanol. Rohdenberg and Nagy, in 1937, attempted to study growth promotive and inhibitory fractions in human urine.Around the same time Turner used similar fractions of normal human urine and concluded that putative growth promotive fraction had no specific effect on the rate or type of tumours induced by chemical carcinogens [1]. Instead, he did observe a significant retarding effect on tumours from the growth inhibitory fraction when given over a long period. Bowman and Mottshaw pursued what at that time could best be called indeterminate results on the effects of urinary extracts. In their study, they used ether and benzene extracts of urine from cancer patients. Their experiments were of a long duration, with a 250 days follow-up period and their results indicated no tumour-promotive effect in urine extracts of cancer patients. Sobotka and Bloch, in a study of 150 days durational so found no tumour-promotive activity in the extracts of urine from cancer patients. What has emerged from most of these studies is that there was no consistent

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growth-promotive effect of the extracts of urine from cancer patients. However, there is a need to critically evaluate why tumour regressive activity in urine reported in some of the other studies.

LITERATURE REVIEW

Are there carcinogenic substances in human urine?

A variety of urinary extracts from normal subjects and cancer patients (non-endocrine cancers) for carcinogenic effects. Even at very high doses of the concentrated extracts, equivalent to 5-15 litres of urine, administration of the neutral and alcohol–insoluble fractions of the benzene extract as well as the petroleum ether soluble fraction of the alcohol- insoluble fraction did not induce a sarcoma at the site of subcutaneous injection in mice. In the same study, when butyl alcohol extracts were injected at far lower doses (equivalent to 80-125 ml of urine), sarcoma was induced in one mouse with the extract from cancer patients and in two mice with butyl alcohol extracts of urine from normal volunteers. These sarcomas did not exhibit the feature of aggressive sarcomas induced by the other chemical carcinogens. Their relative non-invasiveness was very different from the tumour progression seen after chemical carcinogenesis. What can be gleaned from this study and those of Turner as well as Bowman and Mottshaw is that there does not appear to be any real tumour growth-promotive effects of the different types of urine extracts from cancer patients.

Waning of interest in tumour-growth regulators

The interest in the possibility that there are innate growth regulators of tumour in the tissue and the body fluids waned for almost two decades. Albert Szent-Gyorgyi's work rekindled the interest in tissue/ body fluids extracts and modulation of cellular proliferation. His experiments led to the isolation of two fractions from the thymus. He named these fractions as (a) promine, with a malignant growth-promoting action and (b) retine, with a retarding effect on, subcutaneously transplanted Krebs 2 ascites tumours. However, isolation of the hypothetical molecules from the fractions that mediated these effects proved elusive, despite the observed biodynamic effects and chemical analysis of the two fractions, with the-then technology.

Are there tumour-inhibitory substances in urine?

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Are there tumour-inhibitory substances in urine?

Williams and Walters, in a landmark paper, reported tumour-inhibitory effects of urine extracts. They tested a large number of urine extracts and isolated the growth-inhibitory effect in a crude fraction of urine which had been acidified to pH 4 and then continuously cold extracted with toluene. Following charcoal and alumina adsorption, a purified active extract was confirmed by chromatographic analysis and the aqueous alcoholic fraction retained the growth inhibitory activity after partitioning with 60% alcohol. The dissolved solids, buffered at pH 7, were injected as daily doses of 0.4 mg intra-peritoneally into mice with Twort Alveolar Carcinoma. Sixty-eight tumour bearing mice were injected with the urine extract and served as the experimental group. The control group had forty-six mice, treated with saline. The regressive effects of the urine extract on tumours were observed as early as on the fourth day, with no influence on the baseline size of the tumours in the controls. The attempts at chemical isolation from the active extract failed to give significant biological results. The activity on storage, being prone to the rapid oxidation, was unstable due to a short shelf-life. Such instability is a challenge as well as an opportunity for molecular isolation and identification state-of-the-art analytical methods like LC-MS-MS and GC-MS-MS.

Szent-Gyorgyi has vividly traced the story of retine in his famous book -"The Living State- With Observations on Cancer". Indeed, persistent attempts were made to purify urine extracts and concentrates and to identify the chemical nature of retine [2]. However, the precise structure of this "retine" eluded the investigators. It was known that its UV absorption had maxima at 272nM in water at pH 7, with a pH-dependent shift in absorbance to 292 nM at pH 10. Hence, Egyud and Szent-Gyorgyi ascribed the tumour-regressive activity to ketoaldehydes. Aliphatic ketones often exhibit absorption maxima at 272nM and they explained the shift in absorption maxima as a consequence of keto-enol tautomerization. Szent-Gyorgyi and colleagues went to pursue ketonic aldehydes as the putative retine, further bolstered by the information that aldehydes do exert tumour inhibitory effect. This had been demonstrated as early as 1938 by Strong and Whitney. Egyud identified Methylglyoxal (MG) in one if their "retine" preparations.

The quest for retine then took a detour into the alluring path of chemical synthesis of the homolog series of MG and its various cyclic derivatives. However, the tumour-regressing activity of the molecule was not specifically pursued. Instead, α-keto-β- ethoxy butyraldehyde, called ketoxal, was shown to interact with the guanine of nucleic acids by Staehelin.

Sub-molecular theory of cancer and the glyoxalase system

Szent-Gyorgyi had proposed a theory to support the role of glyoxalase in cancer vis-à-vis the purported retine. Despite a plausible role of MG having been delineated by earlier evidence there were several pros and cons to this theory. Kalapos reviewed Szent-Gyorgyi's sub molecular theory of cancer and was unable to marshal sufficient evidence in favour of retine.Kalapos revisited this same topic six years later and rediscussed the promine-retine theory. He stated that though the glyoxalase system was discovered in 1913 its function and the role of MG have been debated. Kalapos summarised that given the promine-retine theory had no therapeutic impact it should be dropped. The conclusion added further to the lack of scientific interest that was crucial to the follow up of the initial robust observations of the retine and the other cancer-inhibitory urine extracts.

Urinary peptides, amino-acids and derivates; antineoplastons

Burzynski, a Polish scientist, while renewing the history of antineoplastons stated, "Medicinal use of urine and urine extracts has been known for centuries in ancient Egypt, Greece, Rome, India as well as in North and Central America ". Antineoplastons are urinary peptides which have antiproliferative effects on cancer cell lines. In 1897,Bondzynski initiated research on the anticancer activity of urinary peptides. Despite misgivings on those findings and varying success with their own attempts, the group persisted in the studies on antineoplastons. More recently, a Japanese group has shown that A10, the naturally occurring peptides and amino acid derivatives of antineoplastons from urine, markedly inhibits proliferation in a breast cancer cell line (SKBR-3). They also showed that there was a cell cycle arrest in G1, likely to be mediated through an increased expression of p16 and 21 proteins. Their studies revealed a down regulation of protein kinase Cα and an inhibition of MAP kinase signalling. The authors stated, "Our findings indicate that the antitumor effect of antineoplastons -A10 could be utilized as an effective therapy for breast cancer.

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Ureterosigmoidostomy in human and cancer regression

Hammer in1929, reported for the first-time occurrence of cancer of the sigmoid colon after ureterosigmoidostomy for extrophic bladder. There were several reports of adenocarcinoma of the colon after ureterosigmoidostomy. One of the views was that there was colonic exposure to carcinogens as well as growth factors such as epidermal growth factor in urine. The use of ureterosigmoidostomy for cancer of the bladder, offered opportunities to observe the effect of urinary diversion on the state of the bladder tumour, as the urine now also got partially absorbed from the colon. In 1964, Tilden Everson at a meeting of the New York Academy of Sciences reported a large series of spontaneous regression of cancer.

In their series of 176 cases of spontaneous regression, 13 were patients with bladder cancer. Post-ureterosigmoidostomy, 12 out of those 13 patients showed regression of the bladder cancer. Subsequently cystectomy was carried out in 9 out of 10 patients from day 21 to 6 months. In 4 of these patients, the surgically removed urinary bladder showed no microscopic evidence of cancer. In the other 5 patients, despite a significant regression, there was still evidence of residual cancer.

Everson and Coles explained the cause of cancer regression due to the removal of carcinogen from the urinary stream bathing the bladder. a tumour is already established. It is proposed that the regression observed in bladder cancer is due to a putative anti-cancer substance (ACS). When ACS gets absorbed from the colon, it is suggested that it induces regression by its systemic effect.

DISCUSSION

The Paradox of cancer regression and occurrence

How do we explain the paradox of a rapid regression of the bladder cancer following ureterosigmoidostomy and the same procedure of urinary diversion to the colon resulting in slow developing colonic cancer after a long interval? It is possible that the retine through its systemic action could mediate the rapid regression of the bladder cancer while the local slow- acting effects of promine could lead to the generation of a local colonic cancer in some of the patients. Szent-Gyorgyi had described ketoaldehydes cannot be expected to exert tumour- regressive effects when injected at a distance from the site of the tumour because of their rapid degradation by blood glyoxalase. Ketoaldehydes need to be injected locally for the antitumor effects [3]. One is thus faced with a paradox which currently defies any explanation. More studies are carried on the other urinary precursors of MG and their effects on colonic microbial flora.

The use of urine therapy for health and in cancer

Diverse types of urine therapy have been described in Ayurvedic texts and Bhrigu samhita. In addition, innumerable Ayurvedic formulations are processed from cow's urine. There have been anecdotal reports of efficacy of the distillates of cow's urine and auto-urine in alternative care of cancer patients. Cancer patients attend health care centres and hospitals where cow urine preparations are prescribed [4]. The first world congress on auto-urine therapy was held in India, attended by hundreds of delegates from traditional and modern medicine. The other three nations where urine therapy has been used are England, Japan and Germany. A Japanese scientist Hamao Ilichi, from Kyoto University extracted ruoamalin from human urine that checked the growth of transplanted tumours in mice Novak in a case series, from Germany, reported significant regression of cancer with radiological evidence, in patients on auto urine therapy. In the mid-sixties, Herz reviewed the status and future scope of auto urine therapy. Two patients, with long-term survival and metastatic disease have been reported when treated with autourotherapy and Tinospora cordifolia. There are several books, reviews and articles published on urine therapy in cancer. Sarkar had shown a regression of DMBA-induced breast cancer with urine extract in experimental animals.

Anticancer activity of cow urine, distillate and extracts has been reviewed as to the current status and future directions. Panchagavya, which includes cow urine, has been reviewed for its immunomodulatory and anticancer activity. Cow urine distillate was shown to enhance anticancer activity of Taxol in cell lines. Some case reports have also been cited as examples of therapeutic response to cow-urine in cancer therapy. However, only percentage improvements have been stated without any data on the regression in the tumour mass, duration of survival etc.

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The authors have ascribed the anti-neoplastic effects to be due to the presence of vitamin A, E, C and volatile fatty acids in the cow urine. The same investigators have also carried out *in vitro* studies on the effects of cow-urine on proinflammatory cytokines, phagocytic activity etc.

A Reverse Pharmacology approach for urinary tumour-regression activity

Reverse Pharmacology is a paradigm-shifting approach to drug discovery starting from the bedside to the bench.Historically, many novel biodynamic effects of remedies where observed, often serendipitously at the bedside and then the studies were carried out to discover drugs and their mechanisms of action. Reverse pharmacology would initiate a robust documentation of tumour regression by pharmaco-epidemiology of auto urine therapy in patients. There can be a meticulous, rigorous and long-term follow up of urinary diversion surgery and consequent regression, if any. It is mandatory that the centres that use cow-urinary therapy for cancer patients maintain well designed and appropriate case record forms, duly filled and systematically stored for data analysis. The progression or regression of the primary or secondary cancers should be followed by sophisticated clinical markers as well as imaging, biochemical and/or specific assessment techniques of tumour regression identified for particular tumours. Simultaneously the samples of cow urine distillate and their fractions can be studied *in vitro* for apoptotic/necrotic effects on different cell lines. Diverse ketoaldehydes of biological origin can also be screened. Currently this approach is being pursued by a multisystem and trans-disciplinary team at our Medical Research Centre of Kasturba Health Society.

Future directions in cancer research

As early as in 1909, Paul Ehrlich made quite a prophetic statement “I am convinced that during development and growth, malignant cells arise extensively frequently but in majority of people they remain latent due to protective action of the host. I am also convinced that this natural immunity is not due to antimicrobial body but is determined by cellular factors. This may be weakened in the older age groups in which cancer is more prevalent” Ehrlich’s foresight has been fulfilled by the recent advances in combining immunotherapy and targeted therapies in cancer treatments [5]. Complete regression has been demonstrated in metastatic cervical cancer and chimerical antigen receptor (CAR) T-cell therapy in a promising new approach to fight cancer.

There have been hardly any studies on the status of T-lymphocytes or NK cells in patients either with spontaneous regression or in those who have shown unusual responses to auto-urine or cow-urine distillate therapy. Relatively less attention has been paid to how and why spontaneous regression of cancer does take place. Lewison, at a conference on spontaneous regression stated “The purpose is to listen more closely and attentively to those ‘whispers of nature’, where by a rare and extraordinary patient with clinically confirmed cancer responds in an unusual and exceptional way without adequate treatment. Perhaps there is more to hear than missed by the ear. With the power of faith in the newest medical research and the prepared perceptiveness ...we may better discern those ‘whispers”.

Concluding remarks

Henry Siegrist has said “All experiments require certain philosophical preparation and I have a feeling that in the case of cancer many experiments were undertaken without the necessary philosophical background and therefore proved useless”. The present review has attempted to provide the philosophical as well as experiential background of some aspects of the biological control of cancer, in light of the examples of regression after ureterosigmoidostomy and rare spontaneous regression of established cancer. It appears that there is already emerging evidence of tumour-regressive activity in biological fluids and urine. However, the repugnance for the practice of auto-urine therapy as a panacea has blanked out any exploration of the rare reports of such cancer regression. The bed-side to bench path of reverse pharmacology can be applied effectively to resolve the paradox of tumour modulation by urine and the other biological fluids.

CONCLUSION

The unstable nature of the anti-tumour activity of urinary extracts and the failure to identify as well as chemically characterize the putative retine pose formidable challenges in research by a reductionist approach. It is desirable to apply an integrative approach along with the state-of-the-art relevant science to explore the biodynamic control of

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cancer. For such an innovative research, a multidisciplinary team with a functional research and development network involving institutions with excellent track record would be essential.

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