

## Anti-Cancer Strategies of Methylglyoxal – A Review

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### ABSTRACT

Methylglyoxal a simple carbonyl compound containing a reactive aldehyde and a ketonic group which stops the growth of cancer cells without poisoning normal cells. It is also called as Retine. These are very small molecules that are highly potent in controlling cell division. This compound inhibits the enzymes required for cancer cell and infected cell to grow by respiration and does not harm normal cells. As cancer cells require large amount of energy to multiply which was provided by ATP. Methylglyoxal inactivates the enzyme Glyceraldehyde-3-phosphate Dehydrogenase (GA3PD) needed for the ATP production in cancer cells and there by starves the cell to death and normal cells remain unaffected. As it is a carbonyl group, it inhibits the mitochondrial respiration followed by Glycolysis and Krebs's cycle which play a major role in the production of ATP and supplies the energy to infected cell up to demand. It also play a role in binding of oxygen at cellular level and preventing the proteins to desaturate and inhibits the production of free radicals. Hence suitable energy and oxygen are unavailable to cancerous cell to grow, leading to death of the cell. It was believed that "If cancer cell cannot grow, it dies by itself". It desaturate the proteins of malignant cell at cellular level by means of its ketoaldehyde group with an aminoacid of a protein causing the death of cell.

**Keywords:** DHAP, GA3PD, methylglyoxal, MG, retine

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### INTRODUCTION

Cancer, being a dreadful and uncontrollable disease in present society has only treatment but not cure. Cancer is due to the destructive desaturation of protein and DNA leads to mutation and uncontrolled division of cell [1-5]. As several methods and techniques are developed to treat cancer has a wide range of adverse effects leading to reduce duration of patient life time. This is because the cancer therapy may be chemotherapy or radiotherapy is not only damaging the cancerous cell but also the normal cells due to its wide range of side effects. So, research is going on to treat only the tumour but not the other cells. As it is impossible that, if a foreign compound enter in to the body, it is not compatible with the body environment and body irritates leading to side effects. So it became difficult for the scientists to work on the molecules to target the particular cell. Recently several methods are developed which target only the malignant cell by inhibiting the enzymes and

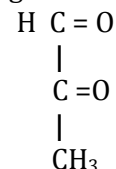
catalysts that help for its growth of a cell. The rational of the study may provide ideas to improve the efficacy of Allopathic system of Medicine and cancer therapy.

Glyoxal and Methylglyoxal commonly called as Retine is a natural compound plays a significant role in cancer therapy. In 1937, Albert Szent Gyorgi, a Nobel laureate, for the discovery of vitamin-C worked on regulation of cancer and identified that Methylglyoxal inhibited the uncontrolled growth of the cell which was published in Science magazine in the year 1963. According to him, methylglyoxal is the primary electron acceptor before oxygen, as it is believed to be an universal acceptor [1]. Methylglyoxal was produced by the nature during the evolution of life on earth. When life originated, the oxygen was not present in free form for the proteins as it is in bound form as water vapour, carbonates etc. Nature achieved it by taking a molecule of water and crowding all the oxygen at one end of molecules, the hydrogens at other end

forming Methylglyoxal causing proteins to desaturate. The brown colour of the liver is due to the slight desaturation of proteins by methylglyoxal [6]. After availability of oxygen these desaturated proteins are used in the origin of life on earth. At cellular level, defective deaturation increase cell division. Retine is normally produced by body, when it is, it prevent growth of cancer. But the body can lose its ability to produce this substance leading to mutation. Putting the Retine back in to the body can stops the growth. His laboratory isolated and manufactured Retine in the year 1967 [1]. Not only Dr. Albert but also scientists like Dr. Egyud and William. F. Koch made a

remarkable approach on Methylglyoxal has anti-tumour activity.

**STRUCTURE:** Methylglyoxal is a carbonyl group with three carbon atoms. It contains an aldehyde group at the first carbon, a ketonic group on the second carbon and hydrogens at the end. These ketoaldehyde group interacts with that of amine group of protein and making it desaturate.



**Figure 1: structure of Methylglyoxal [1]**

### PHYSICAL PROPERTIES:

**Table 1: Physical properties of Methylglyoxal**

Colour	Yellowish hygroscopic liquid
Odour	Pungent
Solubility	Soluble in water, alcohol, ether and benzene
Molecular weight	72.06266 g/mol
Molecular formula	C <sub>3</sub> H <sub>4</sub> O <sub>2</sub>
IUPAC name	2-Oxopropanal
Synonyms	Acetyl form aldehyde, Pyruvaldehyde
Density	1.0455

### CHEMICAL PROPERTIES:

• **Formation of Schiff base:** Methylglyoxal and methylamine are mixed together in aqueous solution. Appearance of yellow color due to the formation of Schiff base. When solvents like acetone or methanol is added purple color appears [1].

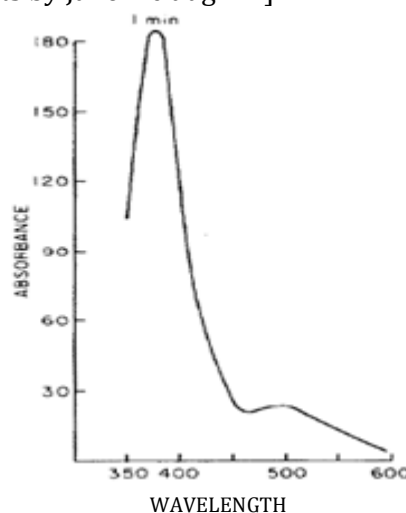
• **Reaction with proteins:**

i) Solution of Lysine is treated with Methylglyoxal which turns in to yellow color [1].

ii) Casein is treated with aqueous Methylglyoxal, Its granules become suspended in the solution and turns yellow. If methanol is added turns to brown. The brown colour of the liver is due to the slight desaturation of proteins by methylglyoxal [6].

• **Absorption spectrum:** Mixture of 0.0256M solution of methylglyoxal and methylamine [0.077M] and 0.0077M ascorbic acid was added, a very strong absorption appears at a wavelength of 400nm and disappears slowly. A second

peak appeared at 500nm [1, Unpublished results by Jane McLaughlin].



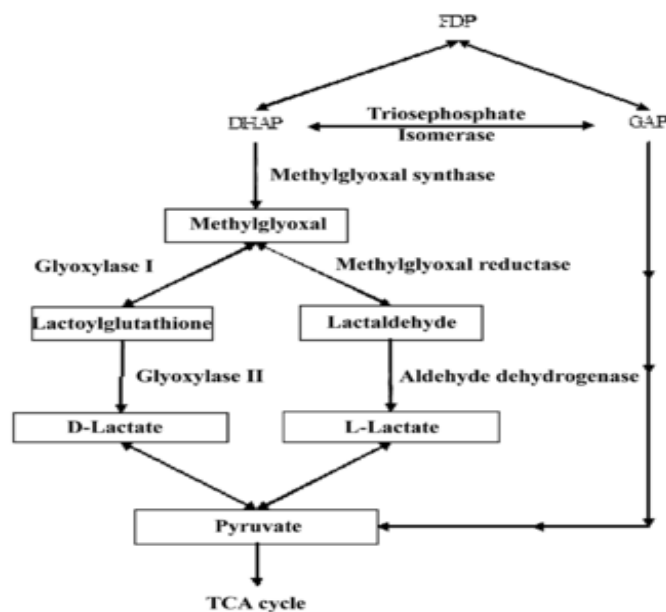
**Figure 1: Absorption spectrum of Methylglyoxal [unpublished results of Jane Mc Laughlin]**

### FATE OF METHYL GLYOXAL IN THE BODY:

Methylglyoxal is produced in the body from glucose as a precursor. This is a parallel

cycle to Glycolysis and Kreb's cycle. Methylglyoxal is synthesized from three carbon containing molecule called Dihydroxy Acetone Phosphate (DHAP) in the presence of enzyme Methylglyoxal synthase. The produced Methylglyoxal inhibits Glyceraldehyde-3-phosphate dehydrogenase enzyme which is important rate limiting factor for the production of ATP. It also reduces the intermediates of Glycolysis and

reduces the generation of ATP in normal body functioning situations. The production of Methylglyoxal in the body is restricted due to the continuous oxidation of glucose in to pyruvate during Glycolysis and Kreb's cycle. It is catalyzed by Glyoxalase system which is a two-step reaction using Glutathione as a coenzyme in which Lactic acid is produced [1].



**Figure 2: Production and metabolism of Methylglyoxal in the body (Un published result)**

**MECHANISM OF ACTION OF METHYL GLYOXAL:** Various theories are postulated on the action of Retine, out of which two of them are illustrated.

**1. Inhibition of Mitochondrial respiration and Glycolysis [7]:** Methylglyoxal acts primarily by triggering a cells oxidative mechanisms to regenerate the impaired aerobic oxygen respiration that causes the cell to develop in to a cancerous. This reduces the formation of free radicals mutation and chain reactions at the DNA level. It is the fact that, cancer cell needs high amount of energy to multiply abnormally which was provided by ATP [7]. It is believed that Methylglyoxal inactivate the enzyme Glyceraldehyde-3-phosphate Dehydrogenase needed for ATP production in cancerous cells by inhibiting glycolysis here by starves them to death without affecting the normal

cells. Recent studies have indicated that mitochondrial complex-1 and the glycolytic enzyme G-3-P Dehydrogenase may be critically altered specifically in malignant cells. Retine selectively inhibition of mitochondrial respiration and glycolysis in human leukaemic cells at lower concentrations [7]. Methylglyoxal strongly inhibits mitochondrial respiration in leukaemic leucocytes, whereas, at a much higher concentration, Methylglyoxal fails to inhibit mitochondrial respiration in normal leucocytes [8]. Methylglyoxal strongly inhibits ADP-stimulated  $\alpha$ -oxoglutarate and malate plus  $\text{NAD}^+$ -dependent respiration, whereas, at a higher concentration, Methylglyoxal fails to inhibit succinate and  $\alpha$ -glycerophosphate-dependent respiration.

## 2. Charge transfer and Electron permittivity [1]:

This theory was postulated by Albert szentgyorgi in his article "Living state and cancer" published in the science journal. Electrons can be taken out of molecules by other molecules by means of a charge transfer. Oxygen is an universal biological acceptor that can accept electrons from proteins and make it desaturate. The higher the desaturation of proteins higher the cell division [1]. Oxygen also important for mitochondrial respiration for the regulation and production of ATP to meet the energy demand of cells to become cancerous. The charge transfer to proteins of mitochondria like SMAC [Small Mitochondria derived Activator of Caspases] binds to IAP [Inhibitor of Apoptosis pathway] and deactivates them, preventing the arresting of cell to degrade. Methylglyoxal a carbonyl compound binds with a bond to oxygen transferring the acceptor power of oxygen to ketoaldehyde group forming Ascorbic acid. Albert szentGyorgi got Nobel Prize for the discovery of Vitamin C. The charge transfer takes place intramolecularly in between methylglyoxal and oxygen in which no net charge develops and formation of free radicals reduces preventing desaturation of protein leading to apoptosis. This charge transfer is referred as "Doping" [1]. This reaction is catalysed by ascorbic acid [Fodoretal., pp. 165-169]. So Vitamin C complex is used along with methylglyoxal as explained above. This theory also supports Otto Warburg's theory of utilisation of energy by the affected cell produced in the oxidative phosphorylation during respiration. This reduces the ROS [Reactive Oxygen Species] and free radicals in the body preventing a tumor to develop.

### METHYL GLYOXAL IN CANCER TREATMENT:

**1. Cow urine therapy [Unpublished results of 18, 19 and 21] :** Cow urine therapy in cancer treatment is gaining popularity in India. Various treatments with much more side effects making people looking in to the windows of Ayurvedic system of Cow Urine Therapy. Many

charitable trusts approved by government of India are now treating the patients using Cow urine therapy which has beneficiary effects without side effects. It was observed that traces of Methylglyoxal is present in the cow urine which was given by research works done by CCRAS and AYUSH. The bioactive fraction of cow urine consists of compounds useful for repairing DNA from the oxidative damages and also Immuno modulating and Bioenhancers [21]. It has anti-cancer compounds such as anti-neoplaston, methyl gloxal [18] in traces amounts but also patented for its ability to efficacy and absorption of anti-cancer drugs of modern medicine and herbal extracts. This therapy has no side effects and reports of increased duration of treated patients. As cow urine is patented for having Anti-oxidant property, and used as a better solvent for the relative absorption of anti-cancer drugs [19]. Traces of methylglyoxal is also reported. These are Ayurvedic formulations used traditionally, a deep research has to be made on these formulations.

### 1.Koch's TMT [The molecular therapy] and MG concentrate [Unpublished result- 20]:

This method was developed by Dr. William. F. Koch in the year 1980. It is composed of homeopathic sized remedies of Methylglyoxal quinine molecules, one of their main functions is their ability to repair damaged respiratory enzymes in cells which is fundamental to the development of cancer. This work was promoted by Dr. Albert SzentGyorgi, a Nobel laureate for discovering vitamin C. TMT uses a very slight amount of Methylglyoxal that states a self replicating process causing the cell and passes on to restore the Methylglyoxal in another cell causing a cascade of cellular response and stopping uncontrolled replication. If cancer cells does not replicate, it will die. Koch's TMT consists of five different formulations of homeopathic remedies of Glyoxal and Methylglyoxal in cells. The five formulations are Parabenzoquinon, Rhodizonsaure, carbonyl gruppen [SSR], carbonyl gruppen, carbonyl gruppen (SSRI) [20]. These formulations produces methylglyoxal in the body and also reduces the formation of free radical formation.



**Figure 3: Marketed product of “The Koch treatment of cancer”**

### CONCLUSION

It was found that leukaemic leukocytes have a high rate of aerobic glycolysis compared with other normal cells, although there is some variation with the type of leukaemic cells which derive most of their energy from glycolysis from many research works, it was observed that Methylglyoxal inhibits both mitochondrial respiration and glycolysis in leukaemic leucocytes, whereas it has no effect on the similar functions of normal leucocytes. Excessive ATP formation in cells also may lead to malignancy. Methylglyoxal inhibits electron flow through complex I of the mitochondrial respiratory chain and inactivates GA3PD in malignant cells, which suggests that in malignant cells are critically altered. It not only inhibits mitochondrial respiration but also reduces desaturation of proteins, reduced production of free radicals. By these anti-cancer strategies of methylglyoxal, it may replace the anti cancer drugs which produce many adverse effects and improves the efficacy of Allopathic system of medicine and cancer therapy.

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