# Botanical Inhibitors of Amine Oxidase: Relevance to Cancer Therapy

**A. Hoffer, M.D., Ph.D.;[1] M. A. Weiner, Ph.D.[2]**

The autonomic nervous system controls physiological responses to stress. Its chemical mediators on the sympathetic side are the catecholamines, dopamine, noradrenalin and adrenalin - particularly the last two. Dr. Cannon's original description of the flight or fight mechanism is still valid. In response to an emergency or a perceived emergency there is a major shock to the autonomic nervous system, releasing a large amount of adrenalin.

However, adrenalin is very toxic and it elevates blood pressure. The body must remove it as quickly as possible. To do so it has developed two main pathways for converting adrenaline to other substances. One pathway leads to adrenochrome, which does not elevate blood pressure. The second pathway leads to non indolic derivatives and is controlled by several enzymes called amine oxidases. Thus, a highly reactive compound which elevates pressure is replaced by other compounds that do not have this property.

But adrenochrome (and the other chrome indoles from noradrenalin and from dopamine) have other properties. Adrenochrome is a known mitotic poison, i.e. it decreases the rate of cell division. In heart muscle and in leukocyte about 80% of the adrenalin is converted into adrenochrome. It is a highly reactive compound with a short half life in the body where it is quickly converted into adrenolutin (3,5,6 tri hydroxy N-methyl indole) which is also toxic, and to 5,6 dihydroxy N-methyl indole which is not. These substances circulate in the body.

In 1967 Hoffer and Osmond wrote, "Adrenochrome markedly inhibits mitotic rate of cells, probably by interfering in the glucolytic cycles.[1] Bullough found that when mice were stressed by overcrowding, the adrenal medulla increased in size 80%. At the same time the epidermal mitotic rate fell 60%. In vitro adrenaline had no anti-mitotic effect on epidermis but when it was injected it did. In contrast adrenochrome was anti-mitotic both in vitro and in vivo. Bullough suggested that during stress the increased quantity of adrenaline was converted into adrenochrome which produced the antimitosis."

This property, antimitosis, suggests that it could be involved in the control of mitosis in the body. It is highly likely that since the adrenochrome is present in the body, it would be used to control excess mitosis, and that it is involved in the prevention of cancer. Nakatsugawa and Sugahara treated 65 patients with lung cancer.[2] They found that AMM (adrenochrome monoaminoquanidine methanesulfonate) and cytochrome C augmented Natural Killer cell activity in nude mice, protected potent NK cells in patients with lung cancer against radiotherapy and sensitized the human lung cancer xenografts to radiotherapy. They suggested that AMM and cytochrome C may have the potential as a differential modulator of radiosensitivity of normal tissues and of tumors. Anti-cancer drugs such as adriamycin may act through an adrenochrome mechanism. They stimulate a redox cycle leading to several free radicals including adrenochrome.[3]

This is the hypothesis which will be elaborated, i.e that too little adrenochrome will increase incidence of cancer while too much will decrease the incidence of cancer. Small amounts of adrenalin are produced all the time even when asleep, but during the day and when exposed to stress, the amount is increased. The continually

1. 3A-2727 Quadra Street, Victoria, B.C. V8T 4E5
2. 6 Knoll Lane, Suite D, Mill Valley, CA 94941

fluctuating level of adrenalin will ensure a constant production of adrenochrome and its conversion to adrenolutin and other indoles. We suggest that this is one of the mechanisms the body uses to deal with excess mitotis. The leukocytes probably destroy abnormal cells by releasing adrenochrome which has the properties of a free radical and will destroy the cell. It is recognized that pro oxidants are needed to destroy cancer cells. Adrenochrome may be the best and safest natural pro-oxidant in the body. This hypothesis suggests a number of testable sub-hypotheses. We will elaborate on one only.

Increasing the formation of adrenochrome will decrease the incidence of cancer while preventing or decreasing its formation would increase cancer development. One method for increasing the formation of adrenochrome would be to increase the conditions which favor this reaction such as increasing the activity of the oxidizing enzymes, decreasing the activity of the other enzymes which convert adrenalin to other non indolic substance. To control cancer one needs two sets of reactions:

(1) Pro-oxidants, e.g. adrenochrome, which are used by the body to destroy the tumor cells. Leukocytes kill by discharging free radicals onto the bacteria or cell they are attacking. Adrenochrome is a natural superb free radical. Normal oxygen levels are needed to maintain aerobic oxidation.

(2) Anti-oxidants, used by the body prevent the formation of too many free radicals. As soon as the free radicals have done their work they must be removed to prevent injury to other cells and tissues.

The adrenalin-adrenochrome system provides a very good means for controlling mitosis. The adrenalin is maintained by repeated exposure to stress. It is converted to adrenochrome and is used by the body as needed and the excess is neutralized by conversion into other indoles which are not as toxic. This is done by the natural anti-oxidants such as ascorbic acid, vitamin E, beta carotene and other anti-oxidants found in food.

Increasing activity of the enzymes which oxidize adrenalin to adrenochrome, i.e. activating the phenolases which catalyze this reaction, will increase adrenochrome formation. Decreasing the activity of amine oxidases by using inhibitors should have this the same effect by forcing more adrenalin into the adrenochrome pathway. Parnate should be a very good amine oxidase inhibitor used in low doses, under 20 mg daily. At this dose level it will rarely cause side effects, may improve mood, and should increase the formation of adrenochrome. I have seen psychotic delirious reactions produced by large doses of Parnate. The effect on adrenochrome production has not been tested. Other amine oxidase inhibitors are Marsilid, Nardil and Manerix.

The alternative literature contains many references to the anti-cancer activity of many natural plant materials or their extracts. It therefore occurred to us that these plant materials may be acting by inhibiting amine oxidases and this could explain their anti-tumor properties. One of us, M.A.W., examined the literature and discovered 41 plant species with amine oxidase inhibitor activity. The question was whether the active plant materials also had anti-cancer properties. M.A.W. cross-referenced 1,312 species looking for anti tumor activity. Just four species demonstrated both amine oxidase inhibition and anti-tumor activity (Table 1, page 85).

The four species with both activities are:

***Licorice***

In vitro water extracts at concentrations of 30 mcg/ml, were found to inhibit monoamine oxidase and xanthine oxidase.[4]

***East Indies Galingale***

In vitro chemical extracts of the rhizome (acetone, benzene, carbon tetrachloride, methylene oxide) at concentrations of 100

| Latin Botanical Name | Common Name | Plant Family |
|---|---|---|
| Glycrrhiza glabra | Licorice | Leguminosaceae |
| Kaempferia galanga | East Indies galingale | Zingiberaceae |
| Myristica fragrans | Nutmeg | Myristicaceae |
| Zea mays | Corn | Graminaceae |

mcg/ml, were found to inhibit monoamine oxidase. The highest activity was found with the benzene extract.[5]

*Nutmeg*

In vivo (humans oral route), 500 mg of seed per person administered 3X daily for a period of three weeks showed monoamine oxidase inhibition. Subjects included four schizophrenic patients and one depressed patient. Four out of five showed improvement.[6]

*Corn*

In vivo, in rats, a diet containing 17% corn oil was fed to one group for two months. Comparisons were made versus another group of rats fed on a low fat diet (4.4% corn oil). The rats fed a 17% corn oil diet showed tyramine oxidase inhibition. Results were measured in gastric mucosa.[7]

**Conclusion**

Owing to the limited nature of the

**Table 1.**
**A List of Botanicals With Amine Oxidase Inhibitor Properties**

| Genus | Species | Genus | Species |
|---|---|---|---|
| Achaetomium | Species | Lathyrus | Sativus |
| Acorus | Calamus | Lophotrichus | Species |
| Ammopiptanthus | Mongolicus | Microascus | pecies |
| Anixiella | Species | Myristica | Fragrans |
| Apiosordaria | Species | Neocosmospora | Species |
| Arachis | Hypogaea | Onygena | Species |
| Arxiomyces | Species | Petriella | Species |
| Catha | Edulis | Pinus | Species |
| Cervus | Nippon | Pithoascus | Species |
| Chaetomium | Species | Pseudallescherichia | Species |
| Cinchona | Pubescens | Rheum | Hotaoense |
| Cordyceps | Species | Salmo | pecies |
| Diplogelasinospora | Species | Sphaerodes | Species |
| Emericella | Species | Talaromyces | Luteus |
| Eupenicillium | Species | Talaromyces | Species |
| Glycyrrhiza | Glabra | Trichocoma | Species |
| Glycyrrhiza | Uralensis | Virola | Elongata |
| Helianthus | Annuus | Virola | Pavonis |
| Hypericum | Brasiliense | Virola | Sebifera |
| Kaempferia | Galanga | Zea | Mays |
| Kernia | Species | | |

anti-tumor screen utilized to determine anti-tumor activity, it is possible that several or many of the plant species in Table 1 may yet also prove to possess anti-tumor properties in addition to their amine oxidase inhibition activity.

This hypothesis suggests that one should look for the most powerful plant - derived amine oxidase inhibitors as potential anti cancer agents. It is interesting that myristicin has hallucinatory properties, and corn diets without enough foods containing vitamin $B_3$ also causes the schizophrenic-like psychosis known as pellagra. It would also be interesting to determine if patients with pellagra have a lower incidence of cancer than non-pellagrins.

**References**


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