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NATURALLY OCCURRING TOXIC SUBSTANCES IN FOODS, WITH SPECIAL REFERENCE TO FAVA AND FAVISM

by

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I. INTRODUCTION

Most of the intoxications produced by naturally occurring toxic substances in foods are medical curiosities because of their rarity or their very limited geographical distribution. It is not the purpose of this review to deal with these, but rather to say something about those that are at present in products that are being used or are potentially useful in the manufacture of weaning foods and to give a more detailed account on the present knowledge on favism. However, for those that are interested in this field, I have compiled a list, which does not pretend to be exhaustive, with references and that is given at the end of the paper in the form of an annex.

II. LATHYRISM AND ODORATISM (1)

Because of their ability to grow in poor lands and to need little water, some species of the genus Lathyrus (sativus, hirsutum, cicera, clymenum, etc.) are used as an important source of protein and calories during wars and famines, or in very underprivileged areas. The high and prolonged intake of these peas occasions, especially in younger adults, a syndrome of spastic paralysis that starts in the legs and cripples the individual after a progressive evolution. Occurrences of this disease were noted in Spain during the Civil War, and it appears in epidemic outbreaks, that sometimes coincide with draughts, in India. The toxic material has not yet been completely identified, although neurotoxic substances have been isolated from certain species of lathyrus (cyano-l-alanine; l alfa, gamma diamino-butyric acid). A considerable difficulty in the study of this disease is the species difference in reproducing the syndrome. Thus, while men and cattle are susceptible, the laboratory rat is resistant.

Another plant of the genus Lathyrus, namely L. odoratus, the common sweet pea, also produces toxic symptoms in man, that can be

reproduced in the rat. The active substances are organic nitriles, i.e. substituted beta-amino-propio-nitriles (BAPN) which produce an alteration in the metabolism of collagen. This leads to defective bone formation that can compress the nerve structures producing a secondary involvement of the nervous system.

III. AFLATOXIN (2)

A number of toxic substances, generically termed aflatoxins have been isolated from a strain of the mold, Aspergillus flavus. Attention was first drawn to this matter, when a high mortality in commercially reared fowl could be traced to certain shipments of mouldy groundnut meal, used in the preparation of poultry feed. Aflatoxins leads to necrosis of the liver with evolution towards cirrhosis and sometimes to primary hepatoma. The importance of aflatoxin in the human species is yet unknown. Aspergillus flavus has also been found in maize, cottonseed meal and sunflower presscake meal. Analysis of aflatoxins is possible today on a routine basis, but the existence of these mycotoxins has somewhat biased the use of peanut meal in the formulation of infant foods.

IV. GOSSYPOL (3)

The pigment glands of the cottonseed produce a yellow substance termed gossypol. This substance, a polyphenolic aldehyde, is toxic to mono-gastric animals. In the seed it exists bound to different materials and also in the free form. Methods for determining free and bound gossypol, are existant and are used on a routine basis for determining it in cottonseed press cake used in the manufacture of animal feeds. Gossypol is known to react with the non peptidic epsilon (free) amino group of lysine, rendering it thus unavailable as source of this essential aminoacid.

The use of cottonseed meal for human consumption relies on a good elimination or binding of the free gossypol, together with a mild thermic treatment so as not to produce protein damage. Gossypol can be eliminated through the cooking of the seed at low temperature followed by a solvent extraction (4). Two other approaches have been tried. One is the extraction of the oil with acetone, in which the gossypol is readily soluble. Another, is the use of a genetic strain of cottonseed that does not have the glands that produce gossypol. This variety of seed has shown promise, but still the commercial value of cotton is more tied to the production of cotton under given cultivation conditions, than to the production of oil or protein from its seed. Cottonseed protein has been used in the formulation of weaning foods in Central America, Peru and India.

V. ENZYME INHIBITORS (5)

The economic importance of soya bean press cake in the commercial preparation of poultry feed, has drawn attention to the problem of the low digestibility of the product in certain insufficiently heated preparations. Inhibitors of trypsin were described in the raw soya beans and in other leguminacea (Phaseolus vulgaris, P. lunatus), the destruction of which by heating was held responsible for the increase in the nutritive value of heated meal. However, not everybody is in agreement with the ascribed role to the "trypsin inhibitor". The excessive loss of sulphur aminoacids, the ones that limit the biological utilization of soya protein, through an increased pancreatic activity, could be the determining factor in the lowered nutritive value of uncooked soya. Thus, certain fractions of the raw bean, are known to provoke a marked hypertrophy of the pancreas in rats. The possibility of a direct action of the "tryptic inhibitor" on the intermediate metabolism of the sulphur containing aminoacids has also been invoked as the cause of the low protein value of raw soya.

VI. RAPESEED (6)

The cultivation of Brassica napus (colza) is in many parts of the world displacing other traditional oilseeds because the resistance of this crucifera to climatic stress, low water supply and poor soil conditions. The quality of rapeseed oil is lower than that of groundnut, maize or sunflower, but the high yields obtained compensate for the lowered price. Also, the high content of erucic acid has been claimed to reduce the nutritive value of protein, to increase the cholesterol levels and to inhibit growth.

Rapeseed presscake is probably the cheapest of the oilseed meals, because its use as animal feed is limited by the presence of toxic materials, which renders its inclusion into poultry feeds not advisable and into cattle food not recommended beyond 10%.

It has been known for some time that cattle that feed on colza develop goitre and a decreased rate of growth. Rapeseed contains a number of glucosides that include sulphur in their aglycone, being termed thus, thioglucosides. The seed also contains an enzyme, myrisinase, that is able to hydrolyze the glucosides into their components: one molecule of glucose, one molecule of sulphate and one molecule of substitued isothiocyanate. Six glucosides have been identified, the most active being progoitrine, whose aglycone hydroxy-2-butenyl-3-isothiocyanate cyclates into the potent goitrogenic vinyl-5-oxazolidine-thione-2.

It is known that the aminoacid composition of rapeseed is good, exhibiting a chemical score of about 80. However, because of the toxic materials present, the actual value is much lower, when given to animals. There are methods available and in use to destroy the enzyme myrisinase, and the treated rapeseed is successfully employed in the formulation of poultry feeds. However, much remains to be done. Recently, a method

for detoxyfying rapeseed meal through extraction of the glucosides, rather than the inactivation of the enzyme is showing great promise, and values of Net Protein Utilization of about 70 have been claimed for the treated product (7). An adequate technology of rapeseed to render it safe and non toxic, could make enormous quantities of protein available for human use.

VII. CYANOGEN (8)

A large number of plants used as human food contain glucosides that on hydrolysis liberate toxic amounts of prussic acid. These include cassava, sorghum, linseed, bitter almonds, cycads, yams and pulses. The normal culinary procedures used in the traditional preparation of pulses, i.e. soaking and prolonged cooking, are known to render these products safe. However, the inclusion of pulses in industrialized foods, such as weaning foods or legume purees, should take into consideration the potential hazard of insufficient treatment. Instances of moderate poisoning with inadequately treated P. vulgaris dehydrated puree have been communicated (9). It has also been shown that the amount of cyanogen present varies considerably not only from one species to another but within varieties of the same species. The mixing of dry powders offers a cheap way of manufacturing weaning foods from milled pulses. It should be remembered that the soaking process will then be left out. It is thus possible that the amounts of cyanogen left in the product as being fed to the babies, will not be minimal and might constitute a health hazard. It seems advisable that all products manufactured from pulses known to contain cyanogenic materials be guaranteed to have only a minimal amount of residual prussic acid.

VIII. FAVISM

The high content of protein in fava beans and its low price, makes it a valuable element in human diets. Also, the possibility of employing

fava in the formulation of protein-rich-mixtures has been receiving considerable attention from food technologists and nutritionists. However, it has been known since ancient times that the ingestion of fava can produce a fatal illness in susceptible individuals.

Favism is a hemolytic disease provoked in certain susceptible individuals by the contact with Vicia fava. It is currently held that favism can be produced by:

1. eating fresh raw beans
2. eating fresh cooked beans
3. eating cooked dry beans
4. through mother's milk in breast fed children
5. walking through a field planted with fava (Inhalation of pollen?)
6. handling the plant or the bean.

The disease (generally, but not always) starts soon, sometimes hours later, after the contact, with chills, weakness and pallor. Hemoglobinuria followed by jaundice appears in some cases as a result of massive intravascular hemolysis and counts of less than 1.000.000 red blood cells per mm^3 can be found. Death can occur from acute anemia if blood transfusions are not given in time.

It should be pointed out that favism is not always a dramatic disease and "abortive" forms do exist and could be widespread. A well documented case of this form has been related by J.E. Bowman in Shiraz (Personal communication). A laboratory technician known to be G6PD deficient complained of headache. Upon clinical examination a slight jaundice was noted and a red cell count showed a small drop. On interrogation she said that she had eaten fava beans the previous days, but that she had been eating them all her life without any trouble. The jaundice disappeared in the next few days and her red blood cells returned to normal.

The disease shows a marked preference for children, especially under four years of age. It has a male/female ratio of 3 to 1 and generally shows a marked seasonal prevalence. This latter is very true for favism as it occurs in Iran (10,11), but is not as marked in other parts of the world where the disease exists (12).

In the pathology of favism, important knowledge has been obtained in the last ten years.

It has been known for some time that certain drugs, notably primaquine, could induce hemolytic crises in certain susceptible subjects. No immunological abnormality was linked to this disease, but some defects in the red blood cell could be shown to exist. Glutathione levels (reduced form GSH) were found to be lower in these individuals. On receiving the drug, the level of GSH was found to drop considerably. A relationship between the occurrence of favism and drug sensitivity was described by Sheba (quoted by Szemberg, 13) in Israel and the same genetic abnormality was postulated in both diseases. Italian authors (14) showed that favism as well as drug-sensitive hemolytic patients had lower than normal GSH levels in the erythocytes.

Investigations carried out by Carson, Schrier and Alving (15) showed that red cells from primaquine-sensitive individuals had the added defect of low concentrations of glucose-phosphate dehydrogenase, (G6PD), and enzyme of the pentose pathway of carbohydrate metabolism. This enzyme is responsible (diagram 1) for the transformation of glucose-6-phosphate into phosphogluconic acid. The hydrogen carrier in this reaction is triphosphopyridine nuclectide (TPN) and in this transformation one molecule of reduced TPN ($TPNH_2$) is formed. A further molecule of this hydrogenated nucleotide is produced through the succeeding steps of the metabolism of phosphogluconic acid to ribulose.

It should be remembered that the red blood cells do not contain the enzymes of the citric acid cycle and that the only possibility of producing $TPNH_2$ is then through the pentose shunt.

$TPNH_2$ is the necessary coenzyme in the reduction of the oxidized form of glutathione (GSSG). Therefore, without $TPNH_2$ glutathione will remain in the oxidized form. Increased levels of oxidized glutathione in G6PD deficient patients has only very recently shown to occur (16). If reduced glutathione is necessary for the prevention of hemolysis and/or the maintenance of the structure of the red cell, hemolysis would follow the depletion of $TPNH_2$.

Exactly how normal levels of reduced glutathione prevent hemolysis is not known, but it has been theorized that oxidizing compounds cause hemolysis.

The known role of $TPNH_2$ in the synthesis of lipids could account for alterations in the membrane of the red blood cell, explaining perhaps an increased sensitivity to hemolysis.

Genetically G6PD is sex-linked to the X chromosome, with traits of intermediate dominance and "variable gene expressivity". Two genotypes of individuals are possible in relation to G6PD in males and three in females (male: X normal Y, X altered Y, females: X normal X normal, X altered X normal and X altered X altered).

The genetic mosaic theory could explain why widely different enzyme activities can be found in different subjects.

There are, however, many facts of these problems that remain obscure, even in the light of the above explained new knowledge:

1. Why is the hemolysis induced by fava so much quicker than the drug-induced hemolysis (hours vs days)?
2. Why are small children so much more susceptible to favism than adults and why the disease is of a graver nature in this age group?
3. Does contact in other ways than eating, really induce favism?

4. What are the active principles in fava to which certain individuals react?

The last question seems to be the most important from the practical point of view, because by identifying the active substance, we could find out:

(a) how to destroy it: cooking time, temperature of cooking, sun-drying, special chemical agents, etc.

(b) new genetic strains of Vicia fava that would be low in this toxic substance.

IX. TOXIC FACTORS IN FAVA AND THEIR POSSIBLE ROLE IN DETERMINING FAVISM

The role of toxic substances present in fava in determining favism has not received very much attention. Furthermore, some of the clinical and epidemiological characteristics of favism seem difficult to explain on basis of classical toxicity.

Many physiologically active substances have been isolated from fava beans (17) (aminoadipic acid, carbamide, dihydroxiphenylalanine, kaempherol, convicine, vicine, divicine) but the ones that have received more attention are·

1. The glycoside vicine and its aglycone divicine
2. Dihydroxiphenylalanine (DOPA).

1. Vicine and Divicine.

The glycoside was first isolated from Vicia sativa (vetch) by Ritthausen in 1876 but has also been found in beet juice and peas. Its chemical structure was determined by Bendich and Clements (18) as 2, 4 diamino-6-hydroxipyrimidine 5- (beta-d-glucopyranose) (see diagram 2). The glycoside has been extracted from fava by Lin and Ling (19) using 65% ethanol followed by precipitation with mercuric sulphate. Vicine is separated as colourless prysmatic crystals which become brown on aging.

Divicine can be prepared from the glycoside by acid hydrolysis. Vicine and divicine react with the Folin-Ciocolteau phenol reagent.

The content of glycoside found by Lin and Ling (17) is about 5g. per kg. These authors (19) have also shown that when vicine is added to a rat diet at the level of 0.6g. per kg. the weight gains over 41 days are lower than in a control group. However, the groups tested by these authors were only of three males and three females of considerably different initial weights. The only toxic effect, apart from a discreet lowering of the food intake and rate of growth, was a loss in hair of the male rats that received the glycoside. Vicine was also studied in dogs (19) that were given the glycoside by mouth in a dose of 0.2g. per kg. of weight. The first two fractions of urine passed by the animals showed evidence of occult hemoglobinuria. The same authors (20) have shown that inhibition "in vitro" of G6PD activity from a homogenate of normal human red blood cells occurs to an extent of 38% when incubated with vicine at a concentration of $5x10^{-3}$M. Divicine shows no such effect.

This concentration seems to be quite high because one litre of the incubating solution contains 1.5g. of the glycoside. For a blood volume of 9 litres this would mean a total of 12g. This quantity is present in more than 2kg. of fava beans, an improbably high intake.

2. 3,4 Dihydroxyphenilalanine (DOPA)

DOPA in the free state (21) and coupled to glucose (22, 23) have been found in Vicia fava.

The possible role for DOPA in favism has been examined by Kossower and Kossower (24). These authors incubated normal blood and blood from G6PD deficient subjects with DOPA. Normal blood did not experience a fall in GSH content of erythrocytes. However, there was marked decrease in the content of this compound in the red blood cells of G6PD deficient subjects.

Similar effects have been shown by L. Businco and co-workers (25) using an organic solvent extract of fava beans. Also Walker and Bowman (26) working in Shiraz, found the same thing to occur with aqueous extracts from the beans, the pollen and the pistils of Vicia fava. The bean extract lost this effect on boiling (27).

Kossower and Kossower (24) point that only some G6PD deficient subjects are prone to favism and that genetic factors (of an unspecified nature) can play a role in determining the actual hemolytic disease.

The related work offers the following questions to be answered by future investigators:

1. Does the amount of these substances (vicine, divicine, DOPA and its glycoside) change very much according to the variety of fava, the time of the harvest, or other factors?
2. Does the blood G6PD deficient subjects react differently to these compounds if the blood is from an individual prone to favism than from one that is not?
3. Is the DOPA glycoside more active than DOPA (in the same way as vicine is more active than divicine)?

Legumes are known to contain different toxic substances such as trypsin inhibitors, hemaglutinins (5) and cyanhydric acid (8) most of which are destroyed by the heating involved in the ordinary culinary procedures. Some of these factors have also been identified in fava, but their presence has not been systematically explored in this food material.

The presence of hemaglutinins in fava has been studied by Greggor and Gifford (28). These authors have reported that fava bean extracts are capable of producing hemaglutination of human and animal red blood cells and that this effect can be increased a hundred-fold by adding

gum accacia to the medium. An interesting finding by these same authors is that human serum inhibits this agglutination and that this effect is contained in the gamma globulin fraction of the serum proteins. The authors regret that they have not been able to test this property of the fava vis à vis the blood and serum of patients suffering from favism.

The discrepancy between the amount of fava eaten (or its production by inhalation) and the appearance of favism is referred to by all authorities, pointing to the possibility of the disease being of an immunological or allergic origin. Intradermic reactions with fava extracts have been reported in the Italian literature (12) and Kantor and Arbessman (29) have found antibodies to fava beans in subjects suffering from favism. These authors have also shown that hemaglutinins to fava bean extracts can be induced in rabbits by feeding the animals on a fava diet (30).

Quite another problem is the traditional flatulence induced by the consumption of beans generally and of fava beans especially. This proverbial property has been recently tested in rats and human beings and found to be evident and of considerable magnitude (31, 32). This effect is somewhat diminished by cooking, is not due to the cellulose content of the beans and is little affected by the administration of antibiotic.

The production of flatus by fava and other beans should be further studied, because their large-scale use and general acceptance can be limited by this undesirable property, especially in a high protein mixture intended for weaning.

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A tentative list of food materials that contain, or can be contaminated with (*), naturally occurring toxic substances. With references.

Animal Foods

1. Naturally-toxic fishes. Example: Puffer-fish poisoning. Mosher, H.S. et al. Science 144:1100, 1964

2. Fishes that can become toxic through eating certain algae, anelids, coelenterates, but that are not normally poisonous. The "ciguetera" syndrome in the Caribbean. Isel, J. Rev. Hyg. Med. Sociale 12:525, 1964. Nigrelli, R.F. Ann. Ny. Academ. Sci. 90:615, 1960

3. Shellfish, mussels, clams, oysters when they feed on the dynoflagellate Gonyaulax catenella and provoke the "paralytic shellfish" poisoning. Nigrelli, R.F. op. cit. Oftebro, T. Nord. Vet-Med. 17:467, 1965

4. Poisonous turtles in the Indian Ocean. Pillai, V.K., Nair, M.B., Ravinranathan, K., Pitchounoni, C.S.J. Assoc. Physicians India 10:181, 1962.

5. Certain matured cheeses when eaten by people receiving monoamine-oxidase inhibitors (antidepressant), through inability to metabolize tryptamine. (Doeglas, H.M.G., Huisman, J. and Nater, J.P. Lancet ii, 1369, 1967

6. Honey. That produced where toxic plants are abundant. Vop. Pitam. 24:65, 1965. Carey, F.M. et al. J. Pharm. Pharmacol. 11:269T, 1959

7. Eating the flesh of animals that have consumed poisonous alkaloid or glycoside-bearing plants.

8. Polar bear liver, through the ingestion of massive dose of Vit. A

Vegetable foods

1. Lathyrism and odoratism (reference in the text)

2. Favism (reference in the text)

3. Cyanogen (reference in the text)

(*) with the exception of bacterial products and inorganic materials.

4. Mushrooms, Mickelsen, O. Nutr. Rev. 26:129, 1968

5. Oxalic Acid-containing vegetables, especially rhubarb. Dewberry, E.B. Food Poisoning, 4th Ed. London, Leonard Hill Ltd., 1959, p.247. Lunder, E. Ernaehrung-Umsbhau 13:263, 1966

6. Through conversion of nitrate to nitrates in leafy vegetables (especially spinach) on storing, deep freezing. Metahemoglobinemia. Sinios, A. and Woodsak, W. Deutsch Med. Wochenschr. 90:856, 1965

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8. Bush teas. Responsible for the production of te veno-occlusive disease in Jamaica and the Caribbean area. Nicholls, L., Sinclair, H.M. and Jeliffe, D.B. Tropical Nutrition and Dietetics. Bailliere, Tindall and Cox, 4th Ed. London, 1961

9. Ackee poisoning, through eating the unripe fruits of Ackee (Bighia sapida) which contain hypoglicin that provokes hypoglycemic shock by inhibiting neoglucogenesis. Nicholls, Sinclair and Jeliffe, op. cit.

10. Atriplicism. A Rayneaud-like syndrome, described in China, produced by eating the green shoots of Atriplex littoralis. Nicholls, Sinclair and Jeliffe, Op. cit.

11. Epidemic dropsy. Through the use of contaminated or adulterated vegetable oil with that from Argemone mexicana. Described in India

12. Solanin. Sprouted or improperly cooked potatoes. Atropine-like poisoning.

13. Different cereals, but specially wheat and rye, can be contaminated

    a. by fungi
    Claviceps purpurea and ergotism. Barger, G. Ergot and ergotism. Curney and Jackson, London, 1931. By Aspergillus flavus. Aflatoxin (Reference in the text). In the USSR four different mycotoxicoses have been described that are produced by eating improperly stored cereals or by grain that has been left in the field longer than usual. The two more important diseases are: alimentary toxic aleukia (ATA), causative agent: Fusarium sporotrichoides; and Urov's disease, which is a bone and joint deformation in the young, causative agent: Fusarium porotrichiella. B.J. Wilson, Mycotoxins. Proceedings of the Western Hemisphere Nutrition Congress. op. cit. p.145.

b. by seeds of plants that can have an hepatotoxic effect (Senecio, Crotalaria, Heliotropium). The importance of this at the village level, where flour is locally milled under primitive conditions, remains to be assessed. A. Coady: Human exposure to plant agents capable of inducing cirrhosis and primary carcinoma of the liver. Eighth International Congress on Tropical Medicine and Malaria, Teheran, 1968.

14. Products not normally used as human food: Cottonseed and gossypol (reference in the text); rapeseed meal (reference in the text); peanut meal and aflatoxin (reference in the text).

15. Toxic and undesirable materials present in beans: hemagglutinins (Jaffe, W.G. Arch. Latinoamer. Nutrition 18:203, 1968), which are not of much importance because of termolability; cyanogen (reference in the text); flatulence-inducing substances (reference in the text); trypsin inhibitors (reference in the text).

General References

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2. J.M. Coon and .G. Jaffe Naturally occurring toxic materials. Proceedings of the Western Hemisphere Nutrition Congress, Chicago, 1965, p. 136.

Diagram 1. Pentose shunt in the erythrocyte.

"Naturally occurring toxic substances in foods, with special reference to fava and favism" G. Donoso, H. Hedayat, H. Ghavifekr and H. Khayetian.

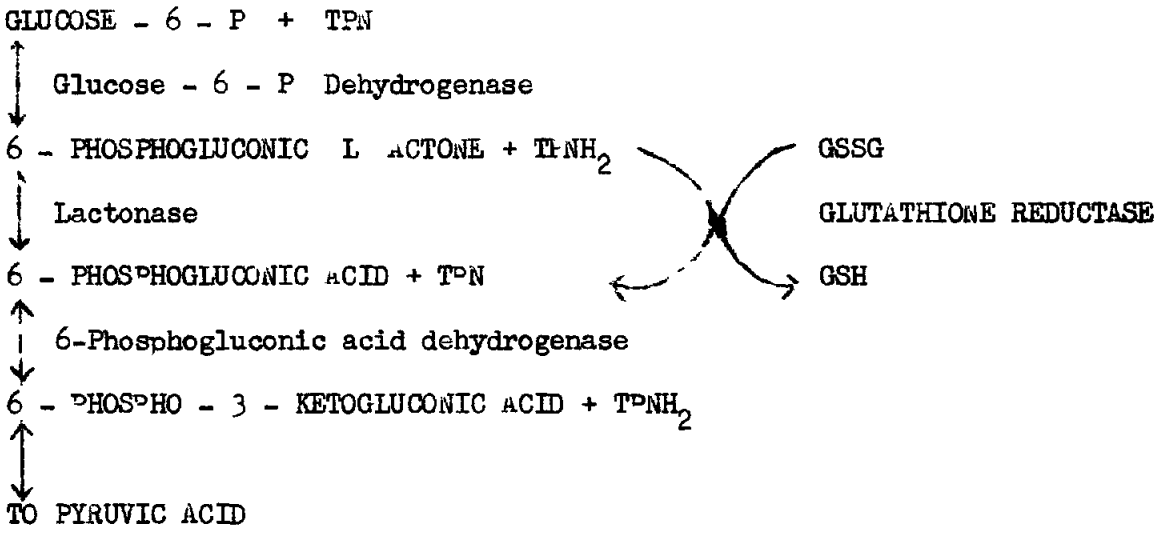

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Diagram 2. "Naturally ocurring toxic substances in foods, with special reference to fava and favism." G. Donoso, H. Hedavat, H. Ghavifekr and H. Khayetian.

DIAGRAM: 2

ACTIVE SUBSTANCES FROM FAVA BEANS

DIVICINE

2,4 - DIAMINO - 6 - HYDROXYPYRIMIDINE

VICINE

2,4 -DIAMINO - 6 - HYDROXYPIRIMIDINE - 5 - (B-D-GLUCOPYRANOSYLOXY)

DOPA

B - (3-4-DIHYDROXYPHENYL) - L - ALANINE

DOPA - GLYCOSIDE

B - 3 - (B-D-GLUCOPYRANOSYLOXY)-4-HYDROXYPHENYL -L-ALANINE

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