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المجلة العراقيه لبحوث السوق
وحماية المستهلك

(ARTICLE REVIEW)

GLUCOSE- 6-PHOSPHATE DEHYDROGENASE DEFICIENCY AND FAVISM

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ABSTRACT

Favism disease, also known as hemolytic syndrome (the breakdown of red blood cells) affects some people (especially male children) when they consume the fava beans (fava bean, broad bean) because they contain high concentrations of pyrimidine glycosides (vicine and convicine) or they take some medications or an imbalance in metabolism or infections. causing the generation of harmful oxygen forms, as these people suffer from a deficiency in the glucose-6-phosphate dehydrogenase (G6PD) enzyme, which is responsible for the availability of, NADPH, which is important in providing reduced glutathione forms, (GSH), as the latter contributes to the conversion of H_2O_2 into O_2 and H_2O, and thus prevents the harmful effects of oxidation in red blood cells, represented by their destruction. Symptoms include nausea, pale jaundice, and dark urine. the severity of the disease varies between patients, and the severity of episodes can vary in the same patient, therefore, diagnosing G6PD deficiency and educating the patient regarding safe and unsafe medications and foods is critical to prevent recurring episodes.

Key words: Vicine, Fava bean, Favism.

الفافزم ونقص انزيم glucose-6-phosphate dehydrogenase

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الخلاصة

مرض الفافزم او ما يطلق عليه بمتلازمه انحلال الدم (تكسر كريات الدم الحمراء) يحدث عند بعض الاشخاص (خصوصا الاطفال الذكور) عند تناولهم الباقلاء بسبب احتواءها على تراكيز عالية من الكلايكوسيدات البيرميدينيه (الفايسين والكونفايسين) او تناولهم بعض الأدوية او حدوث خلل في التمثيل الغذائي او الالتهابات المسببة لتوليد صور الاوكسجين المضر. اذ يعاني هؤلاء الاشخاص من نقص في انزيم glucose-6-phosphate dehydrogenase (G6PD) والمسؤول عن توافر NADPH المهم في توفير صور الكلوتاثيون المختزل (GSH) حيث يساهم الاخير في تحويل مركب H_2O_2 الى H_2O و O_2، وبذلك يمنع مضار الأكسدة في كريات الدم الحمراء والمتمثلة بتدميرها، تشمل الاعراض الغثيان ،الشحوب ،اليرقان والبول الداكن، تختلف شده المرض من مصاب الى اخر كما تختلف نوبات المرض في نفس المريض لذلك يعد تشخيص نقص الانزيم وتثقيف المريض فيما يتعلق بالأدوية والأطعمة الأمنه وغير الأمنه امر بالغ الأهمية لمنع تكرار نوبات المرض.

الكلمات المفتاحية: فافزم، باقلاء، فايسين.

INTRODUCTION

Pythagoras of Samos may have been the first person firmly assert that fava beans may be dangerous and even fatal to humans in the fifth century B.C. (**Chu *et al.*, 2017; Di Meo & Venditti, 2020) ,** he was unaware that the hazard was dependent on the genotype of the individual consuming the beans. This became clear only after G6PD deficiency was discovered in 1956. (**Karafin & Francis, 2019)**. Glucose-6- phosphate Dehydrogenase (G6PD) is the enzyme that catalyzes the first step of the hexose monophosphate shunt., which results in the formation of NADPH. This mechanism eventually protects RBCs from oxidative stress by reducing reactive oxidant species **(Salles *et al*., 2020; Sköld *et al*., 2017).**

G6PD insufficiency is widespread, however it is more frequent in, Southern Europe, Africa, the Middle East, Oceania and Southeast Asia (**Zuccotti *et al*., 2014**). G6PD insufficiency manifest itself clinically in a variety of ways with varying degrees of severity. G6PD insufficiency is categorized as class I-IV by the World Health Organization based on the severity of the G6PD deficiency. People in class II have a significant lack of enzymes, with G6PD activity less than 10% of what it should be. People in Class II have random hemolytic episodes, which usually happen after they are exposed to things that stress oxidants, like fava beans (as in this case) or oxidant drugs. G6PD deficiency can also be categorized by the G6PD gene variants found in certain ethnic groups, such as the class II Mediterranean-type G6PD deficiency. **(Di Meo & Venditti, 2020; Chu *et al*., 2017).**

Although G6PD deficiency is an X- linked recessive condition, most female carriers do not experience the primary clinical signs **(Puspitasari,2017; Prabhu & Rajeswari, 2018**). The two most important parts of favism are the red cell and the bean. Favism defies the conventional division between intraerythrocytic and extraerythrocytic causes of acute hemolytic anemia because it only appears when a person with G6PD-deficient red cells is exposed to specific substances present in fava beans, specifically Vicine and convicine, two - glucosides present in fava beans in high concentrations (up to 2% in dry weight) **(Johns & Hertzler, 2021**).

When fava beans are eaten, the glucosidases in both the fava bean and the digestive tract break down vicine and convicine into divicine (2,6, diamino 4,5-dihydroxypyrimidine) and isouramil (6-amino ,2,4,5 trihydroxypyrimidine), which are then released (Favism induced factors). The antifungal and pesticide properties of these highly reactive redox compounds probably help keep fava beans from going bad, but the compounds can also cause a favism attack (**Karafin & Francis, 2019).**

This article aims to explain the favism disease, the causes of its symptoms, method of diagnosis and the type of food that should be avoided.

Convicine and Vicine

The vicine [2,6-diamino - 4,5 -dihydroxypyrimidine5 - (-D- glucopyranoside)] and convicine [2,4,5-trihydroxy-6-aminopyrimidine 5-(-D-glucopyranoside] are made up of one molecule of glucose coupled to one pyrimidine nucleoside (aglycones) (**Cardador-Martinez *et al*., 2012**). These substances are virtually exclusively found in the legume species Vicia faba, which is a member of the vetch family. Several species of the Vicia genus, such Vicia narbonsensis, have also been discovered to contain trace levels of convicine and vicine (0.1 mg/g) (**Pavlik *et al*., 2002**). The unusual class of antinutritional substances known as convicine

and vicine is almost entirely confined to the genus Vicia. These are the primary causes of the favism medical condition **(Ray & Georges, 2010**).

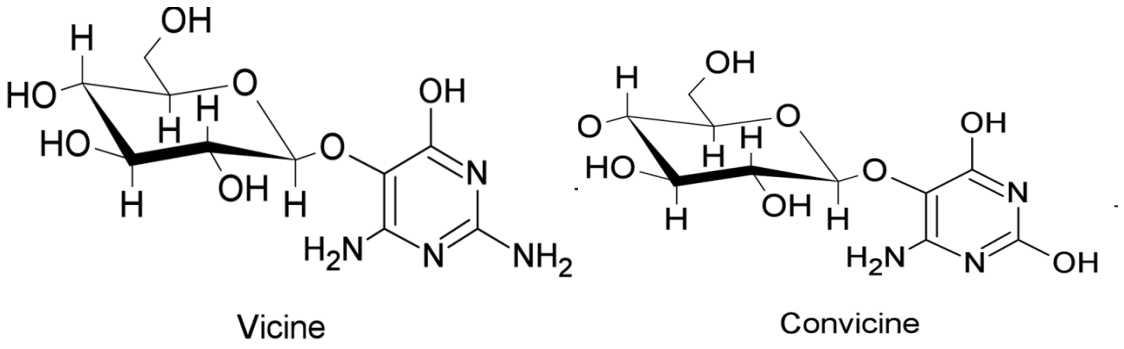

Figure (1): structural formulas of vicine and convicine (**Ray & Georges, 2010**)

How Vicine and Convicine Play a Role in Favism

Vicine and convicine are broken down into divicine and isouramil by -glycosidase, the enzyme made by anaerobic micro flora in the intestinal tract. These compounds are aglycone derivatives, cause favism, a genetic disease that leads to acute hemolytic anemia (**Mckay, 1992**). In natural red blood cells, the oxidative effect of aglycones is quickly taken care of by the effect of compound NADPH, which is the result of the pentose phosphate pathway. But in red blood cells that aren't natural and are sensitive to favism, the effect of compound NADPH can’t get rid of the oxidative effect of aglycones because there isn't enough G6PD and NADPH. So, the aglycones cause change GSH into GSSG (**Multari *et al*., 2015**).

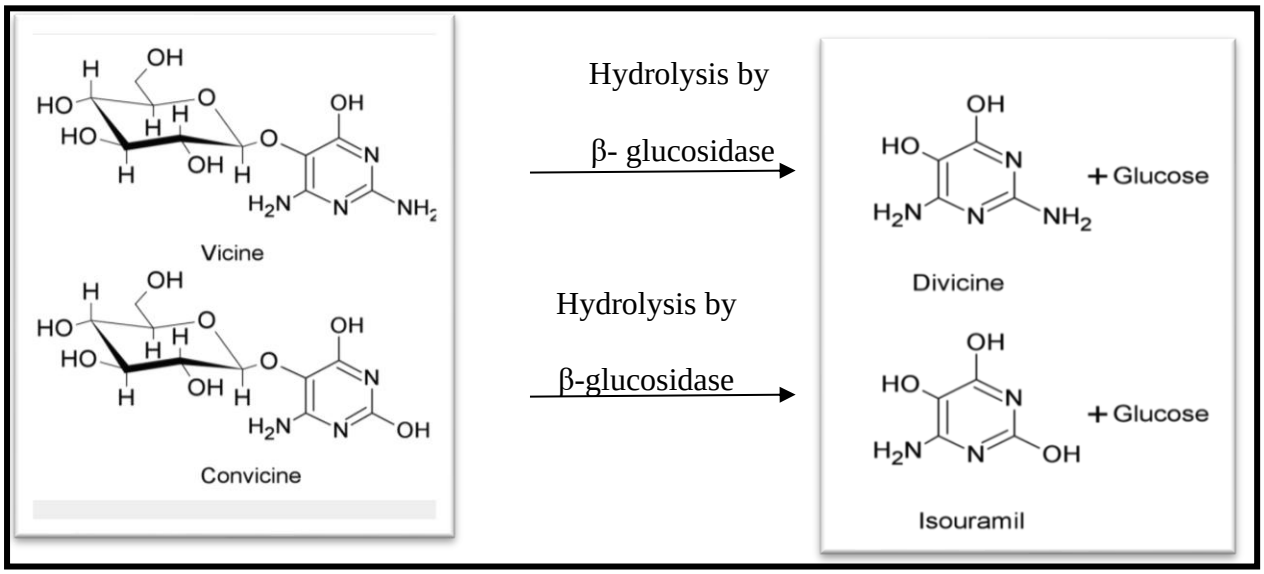

Figure (2): Enzymatic hydrolysis of vicine and convicine to divicine and isouramil (Mckay, 1992).

Glucose-6-phosphate Dehydrogenase Deficiency and Favism

The G6PD enzyme is involved in catalyzing the first step in the pentose phosphate pathway (PPP), which leads to formation of antioxidants that protect cells from oxidative damage. This process produces NADPH, which keeps the reduced glutathione (GSH) inside the cell. Reduced glutathione functions as an antioxidant, protecting cells from oxidative damage **(Luzzatto & Arese, 2018**) (Fig 2).

As a result, a patient with G6PD deficiency is unable to shield their red blood cells (RBC) from oxidative stress caused by several medications, metabolic disorders, infections, or fava bean ingestion (**Cappellini & Fiorelli, 2008**). In the majority of cells, other metabolic pathways support the production of the required intracellular NADPH. In contrast, RBC have no alternative means of producing NADPH.

Thus, G6PD deficiency in RBC results in death. The conversion of oxidized glutathione (GSSG) into the tripeptide known as GSH requires the assistance of NADPH, this tripeptide functions as a reducing agent along with the enzyme glutathione peroxidase for the detoxification of hydrogen peroxide. This mechanism results in the conversion of GSH into GSSG, which lowers the levels of GSH. In the presence of NADPH, glutathione reductase catalyzes the conversion of GSSG to GSH, which results in the regeneration of GSH **(Njalsson& Norgren, 2005**).

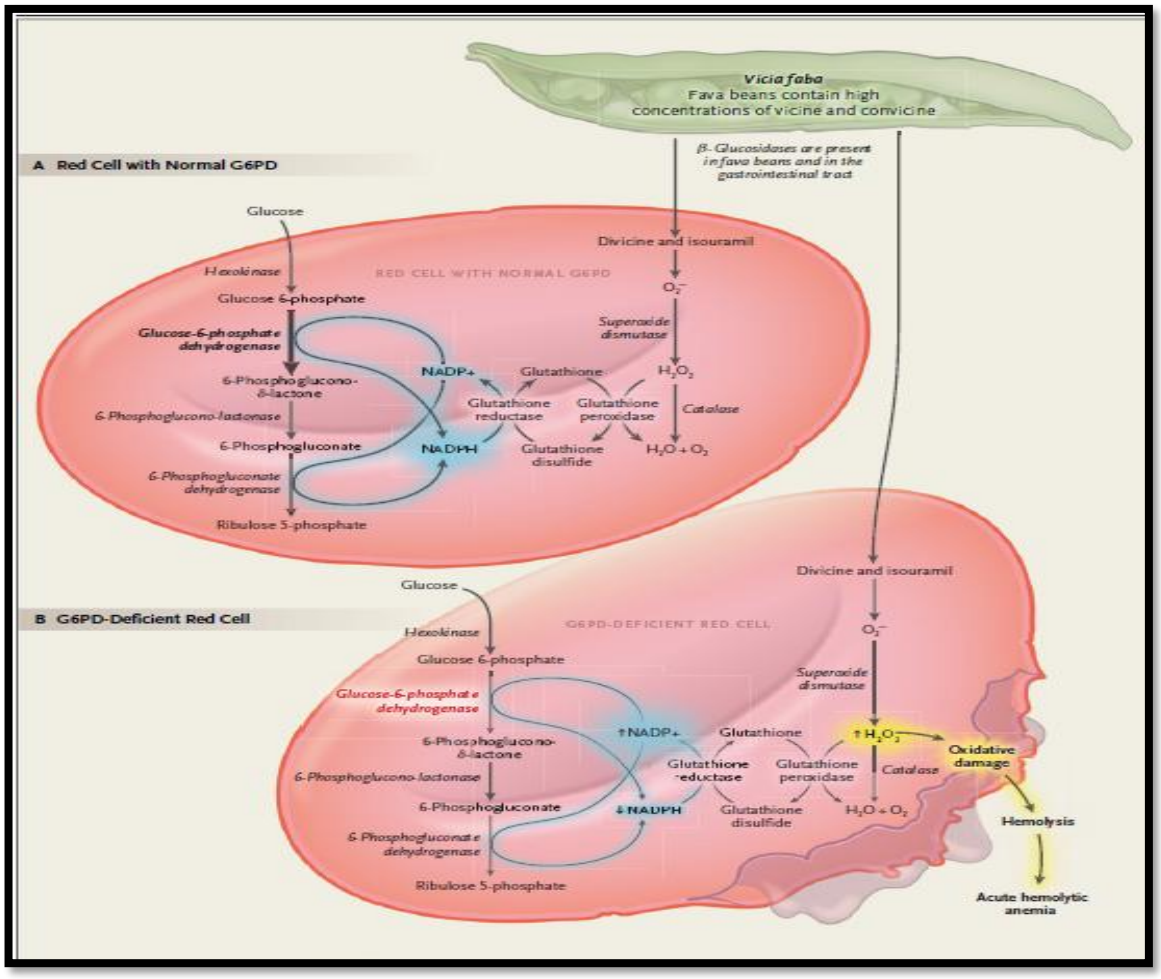

Figure (3): Biochemical role of G6PD enzyme in the cells (**Luzzatto & Arese, 2018**)

Processing is used to eliminate convicine and vicine

Convicine and vicine are stable in heat and water, which makes them hard to get rid of. several studies, most of which focused on soaking (**Jamalian & Ghorbani, 2005; Al-Salmani & Musa**, **2015),** roasting and cooking (**Juma'a, 2010; Cardaror-Martinez *et al.*, 2012**), and fractionation, have looked at how soaking, roasting, and cooking, as well as fractionation, can reduce the amount of vicine and convicine in a plant **(Coda *et al*., 2015).** A number of processing methods, such as enzyme treatments **(Pulkkinen *et al.*, 2016)**, fermentation **(Goyoaga *et al*., 2008),** and germination (**Coda *et al*., 2015; Rizzello *et al*., 2016)**, can cause the hydrolysis of the - glycosidic link. Vicine and convicine are broken down by hydrolysis, but at the same time, the aglycones are released. Most studies have been about getting rid of convicine and vicine, so they haven't looked into how the toxic aglycones are released.

G6PD Deficiency Diagnose

1-peripheral smear

Patients who show signs of acute hemolysis are given this diagnosis. A peripheral smear may show RBCs that have a blister-like appearance (blister cells) and RBCs with Heinz bodies, which are denatured hemoglobin particles that can only be seen with special stains. In individuals with an intact spleen, these cells are removed, thus although they may be evident early in the hemolytic episode, they do not persist (**Ghergurovich *et al*., 2020**).

2-G6PD activity

G6PD activity can be checked but during and right after a hemolytic episode, tests may give false-negative results because of the destruction of older, less healthy RBCs and the production of reticulocytes, which are high in G6PD. So, testing may need to be done again a few weeks after the acute event (**Liu *et al*., 2015).**

Symptoms

Symptoms may appear in 5 to 24 h. Jaundice, dark, crimson urine, pallor, headaches, weariness, fast pulse, dyspnea, stomach discomfort, headache, vomiting, nausea, and a high fever are among the symptoms (**Vottonen, 2018**).

When red blood cells break down, they leave behind a yellow substance called bilirubin. When a person with G6PD has a hemolytic crisis, however, bilirubin levels rise above what is normal. This makes the skin and eyes turn yellow (**Crépon *et al*., 2010).** In severe cases, the symptoms can lead to hemolytic anemia, which is followed by hemoglobinuria.

Types

According to the body's activity of the G6PD enzyme, there are five different types of G6PD deficiency:

Class 1: Chronic hemolytic anemia, with a G6PD enzyme activity under 10%, This indicates that red blood cell degradation is greater than red blood cell regeneration.

Class 2: 10% or less G6PD enzyme activity; disintegration of red blood cells only after being exposed to trigger foods, medications or illnesses.

Class 3: 10–60% G6PD enzyme activity, and the only time symptoms show up is when there are infections.

Class 4: More than 60% activity of the G6PD enzyme, but only mild symptoms.

Class 5: higher G6PD enzyme activity than healthy people, and people often don't know they have this condition because they don't have any symptoms.

Classes one through three are clinically important. This means that when exposed to triggers, there is a high chance of hemolytic anemia, which often needs medical help and treatment (**Crépon *et al*., 2010; Gulewicz *et al*., 2014).**

What to eat and what to avoid

Patients with G6PD deficiency may prioritize eating antioxidant-rich foods to minimize oxidative damage, protect red blood cells, and improve overall health **(Stone *et al*., 2020).** Glutathione replenishment is insufficient in patients with G6PD deficiency, making it essential to maintain vitamin D levels in the body. Current research suggests a relationship between G6PD deficiency and vitamin D levels (**Richardson *et al*., 2021; Subramani *et al*., 2020).**

People with a G6PD deficiency who eat fava beans are more likely to get hemolytic anemia (**La Vieille *et al*., 2019**). Also five-year study of one thousand G6PD-deficient people

showed that the following foods caused hemolytic anemia in some people: broad beans, peanuts, lentils, green peas, black peas, and chickpeas (**Luzzatto & Arese, 2018**).

Substances to avoid using

The following compounds might exacerbate G6PD signs: Naphthalene is a chemical found in home items including mothballs, Toluidine blue is a dye used in several scientific experiments and henna, a plant-based dye commonly used for body art (**Malik *et al.*,2020)**.

drug to avoid

Drug is the least common reason why people with G6PD get hemolytic anemia. But here are the kinds that people with G6PD deficiency should avoid: Diclofenac sodium, Co-trimoxazole, Nitrofurantoin, Dapsone, Acetylsalicylic acid, Rasburicase, Acalypha indica, Ibuprofen, Primaquine, Methylene blue, and Phenazopyridine (**Georgakouli *et al*., 2019).**

Vitamin C (ascorbic acid)

Vitamin C works in the body as an antioxidant that dissolves in water. It can easily get rid of hypochlorite and reactive oxygen and nitrogen species. The products of oxidation with one and two electrons are easy to make again with glutathione and NADPH **(Johns & Hertzler, 2021).**

People who don't have enough G6PD have a less efficient pentose phosphate pathway that turns NADP into NADPH. This uses up the antioxidant glutathione and raises the levels of free radicals and oxidative stress, which break down red blood cells and cause hemolysis. Even though vitamin C is part of the antioxidant defense system, putting erythrocytes in a solution with 0.2mM vitamin C caused oxidative stress and used up glutathione. The pentose phosphate pathway, on the other hand, became more active **(Liu *et al*., 2015).**

In vitro tests with erythrocytes from healthy people and people with G6PD deficiency showed that a solution of 5mM ascorbate alone or in combination with divicine from fava beans increased the production of hydroxyl radical markers, which was then made stronger by the addition of chelated iron EDTA (**Harcke *et al*., 2019).**

CONCLUSIONS

Favism results from a sensitivity to the ingestion of fava beans when red blood cells lack glucose-6-phosphate dehydrogenase, in addition, other substances outside fava beans, such as a broad variety of medications and industrial pollutants, may cause favism in G6PD-deficient people. Children between the ages of two and six are more likely to experience it, and boys are more affected than girls. A reduction in the amount of vicine and convicine is caused by several manufacturing operation, including heating, boiling, and soaking the beans, which lowers the risk of infection. The most common therapeutic intervention is a blood transfusion, and a recovery time of two to three days is anticipated.

RECOMMENDATIONS

The families can be given instruction about the condition and the offending agents of hemolysis., Detailed printed leaflets about the condition and the offending agents should be available in order to be given to the families., Kits for assessing the level of G6PD should be available all through the year, and especially during the fava season, Blood units should be available in a good supply in all pediatric hospitals, in order that the families will not suffer a lot in finding compatible blood for their ill children, laboratory evidence of G6PD deficiency requires particular attention of the public., Health education sessions and further

epidemiological studies are required because early detection and prevention is the key strategy for successful management and control of this genetic disease.

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