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Role of Herbal Medicines in Glucose-6 Phosphate Dehydrogenase Deficiency

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Abstract

Favism is an acute hemolytic reaction triggered in people with an inherited deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD). Glucose 6-phosphate dehydrogenase (G6PD) deficiency is one of the commonest human enzymopathies, caused by inherited mutations of the X-linked gene G6PD. It is estimated that about 400 million people are affected by this deficiency. The G6PD enzyme catalyzes the first step in the pentose phosphate pathway, leading to antioxidants that protect cells against oxidative damage. Most individuals with G6PD deficiency are asymptomatic, with no clinical manifestations of illness unless triggered by certain drugs, metabolic conditions, infections, and ingestion of fava beans. A G6PD-deficient patient, therefore, cannot protect red blood cells against oxidative stresses. Typically, hemolysis ensues in about 24-48 hr after a patient has ingested a substance with oxidant properties. The degree of hemolysis varies with the inciting agent, the amount ingested, and severity of the enzyme deficiency. On the other hand nowadays, more people are frequently turning to herbal medicines as treatments for various medical conditions, often without medical advice. It has been documented that as many patients who take herbal medicine are unaware of their potential adverse effects, so they continue to use the products. The objective of this study examines the herbal medicines that people with G6PD deficient use for other treatments, But their unaware consumption causes symptoms of this disease, so they shouldn't consume them, or about herbal medicines that studies have shown were able to protect against hemolytic damage in human with G6PD-deficient.

Keywords: glucose-6-phosphate dehydrogenase, Favism, herbal medicine

Introduction

Favism is an acute hemolytic reaction triggered by exposure either to fava beans (Vicia faba) or to certain drugs (e.g., sulfa-based antibiotics and the antimalarial primaquine) in people with an inherited deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD). G6PD enzyme generates nicotinamide adenine dinucleotide phosphate (NADPH), which represents the primary defense against oxidative stresses in red blood cells (RBC). Mutations in the G6PD gene can destabilize the enzyme and reduce its activity levels, leaving cells vulnerable to damage from exogenous triggers, including certain foods, infections, and a range of drugs, that may lead to RBC lysis and acute hemolytic anaemia (AHA) (Kattamis et al., 1969). In favism this, the patient can suffer from the destruction of red blood cells, severe anemia, and possibly death. There are two necessary conditions for the disease: (1) genetic inheritance of the "Mediterranean" variant of the abnormal gene trait for G6PD deficiency; and (2) ingestion of fava beans, usually fresh, or exposure to some drugs. The bean is a dietary staple in areas where favism is reported Only an estimated 20 percent of those with the genetic trait for G6PD are likely to experience episodes of favism (Diegues, et al., 2022). Under modern medical conditions the hemolytic anemia caused by favism is only rarely fatal. Strong evidence suggests that both the gene for G6PD deficiency and the cultural practice of fava bean consumption are evolutionarily adaptive traits that protect against death from all types of malaria (Brown., 1981). Favism, then, could be described as a negative outcome of the interaction of the positive adaptive qualities of both the gene and the bean. A consequence of this is that G6PD-deficiencies individuals are resistant the malaria causing parasite (Bienzle et al., 1972). Because G6PD deficiency is an X-linked recessive disorder, the main clinical manifestations are observed in hemizygous males, and most females are unaffected carriers (Schuurman, et al., 2009; Lim et al., 2005). The most frequent manifestations are neonatal jaundice and acute hemolytic anemia, which typically appear 2-4 days after exposure to a trigger, such as certain medications, toxins, or agents of infection (Schick, 2017). Favism is found primarily in the Mediterranean and Middle East regions where fava beans are a staple food and the Mediterranean variant of the G6PD deficiency gene is relatively common. Mark Belsey reports that it is frequently encountered in Greece, Sardinia, Italy, Cyprus, Egypt, Lebanon, Israel, Iran, Iraq, Algeria, and Bulgaria, and is particularly common among Sephardic Jews (Belsey, 1973). The WHO also defines herbal medicines as plant-derived materials or preparations intended for human therapeutic use or further health benefits in humans (WHO, 2005). Herbal products are usually ingested raw, as tea or as decoctions (concentrated extracts). Sometimes they are applied as a paste or powder on the skin. Some herbal traditions, such as traditional Chinese Medicine (TCM) and Ayurvedic

medicine, have medicinal products that are packaged in the form of pills or liquids for ease of consumption and retailing (Ko, 1999). These are sometimes called proprietary medicine, finished products, or patent medicine (Phua, 2009). It has been documented that as many patients who take herbal medicine are unaware of their potential adverse effects, so they continue to use the products. The objective of this study examine the herbal medicines that people by G6PD deficient use for other treatments, But their unaware consumption causes symptoms of this disease, so they shouldn't consume them, or about herbal medicines that studies have shown was able to protect against hemolytic damage in human with G6PD-deficient.

G6PD and G6PD deficiency: historical milestones

Warburg in Berlin, Germany, identified in yeast and in red cells an enzyme of carbohydrate metabolism that oxidized glucose-6-phosphate. Because the oxidation was not carried out by O_2 itself, but required as an intermediary the coenzyme NADP (then called TPN), they named the enzyme Zwischenferment: we now know it was G6PD (Warburg and Christian, 1932). Alving in Chicago, discovered that men who had developed AHA following administration of the antimalarial primaquine had severe deficiency of G6PD in their red cells (Alving et al., 1956). Sansone in Genoa, Italy, found G6PD deficiency in all patients who had a history of favism (Sansone and Segni., 1957). Szeinberg and colleagues in Tel Aviv, Israel, found that the inheritance of G6PD deficiency was consistent with the gene being on the X chromosome (Szeinberg et al., 1958). Panizon in Sassari, Italy (Panizon, 1960), and Doxiadis in Athens, Greece (Doxiadis et al., 1961), identified G6PD deficiency as a cause of severe neonatal jaundice. Shortly after the formulation of the "Lyon hypothesis" regarding inacttheivation of 1 of the 2 X chromosomes in somatic cells of female mice. 1995-2002 Embryonic stem cells in which G6PD had been knocked out by targeted homologous recombination have normal pentose synthesis but exquisite sensitivity to oxidative stress (Pandolfi, et al., 1995); and G6PD inactivation is lethal early in embryo development (Longo et al., 2002).

World Health Organization Classification

The World Health Organization has classified G6PD deficiency as class I-V according to the magnitude of the enzyme deficiency. Patients in class II have a severe enzyme deficiency, where the G6PD activity is <10% of the normal value. Class II patients experience intermittent hemolytic episodes, typically after exposure

to substances that are a source of oxidant stress, such as fava beans (as in this case) or oxidant medications. G6PD deficiency can also be classified according to mutations in the G6PD gene that exist within specific ethnic groups, such as Mediterranean-type G6PD deficiency, which is a class II deficiency (Cappellini and Fiorelli, 2008). (Table 1)

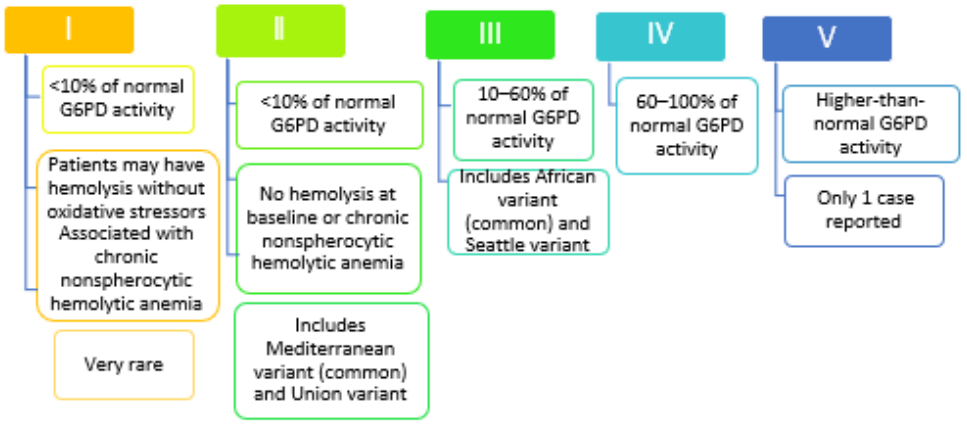

Table 1. World Health Organization Classification of Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency Variants (WHO, 1989).

Herbal medicines cited in the literature

Centaurea ammocyanus

Centaurea species have received considerable interest in biological researches due to their many important biological activities. R. Joujeh et al study *Centaurea ammocyanus* aerial parts hydromethanolic extract for, investigate its hemolytic effect on human erythrocytes and anti-hemolytic activity in the protection of normal and G6PD enzyme-deficient human erythrocytes against oxidative damage. The results revealed that hemolysis caused by *C. ammocyanus* extract was very low with a maximum value of 4.06% at the concentration 3000 µg/ml. The results also showed that the hemolysis induced by H_2O_2 is reduced in a concentration-dependent manner in the presence of the *C. ammocyanus* extract. The highest protection values were about 88.14% and 92.59% for normal and G6PD deficient erythrocytes, respectively. Through this study, it can be concluded that *C. ammocyanus* aerial parts extract showed no obvious hemolytic effect, and could be considered safe for human erythrocytes. The extract had antioxidant activity and was able to protect normal and

G6PD-deficient human erythrocytes against hemolytic damage induced by hydrogen peroxide (Joujeh et al., 2020).

Salvia oficinalls

Salvia oficinalls is an old medicinal plant, which is rich source of different chemical constituents including terpenoids, polyphenol as well as essential oils. Because of its flavoring and seasoning properties, this plant has been widely used in preparation of many foods. In folk medicine of Asia and Latin America, it has been used for the treatment of different kinds of disorders including seizure, ulcers, gout, rheumatism, inflammation, dizziness, tremor, paralysis, diarrhea, and hyperglycemia (Garcia et al., 2016). In traditional medicine of Europe, *S. officinalis* has been used to treat mild dyspepsia (such as heartburn and bloating), excessive sweating, age-related cognitive disorders, and inflammations in the throat and skin (Perry et al., 1999; Adams et al., 2007). German Commission E has accepted the use of *S. officinalis* for a number of medical applications included inflammation and dyspepsia. *Salvia officinalis* extract is used to stabilize fat and fat-containing food against oxidation. The main antioxidant compounds in the sage are carnosic acid and carnosol rosmarinic acid. Al-Awaida showed *Salvia oficinalls* extracts were able to protect hemolysis in parallel to their activation extents on G6PD activities (Al-Awaida and Akash, 2014).

Diospyros lotus L

Diospyros lotus L. is indigenous to the temperate Asian forests, China and also seen in north of Iran from parts of the coast of Caspian Sea up to 1100 meter from sea level in Astara to Ramian, Gorgan in north of Iran (Mallvadhani et al., 1998). *Diospyros lotus L*., similar to other species of *Diospyros*, has a high amount of naphthoquinones especially 7- methyljuglone. Many studies have shown that it has numerous biological and pharmacological properties include: including its use as an antifebrile agent, secretions, as a sedative, and for controlling cough (Sabeti, 1997). Azadbakht et al evaluated the protective effect of *Diospyros lotus L*. fruit extract against the hemolytic damage induced by Vicia faba beans extract in both G6PD enzyme-deficient human and rat erythrocyte in vitro and in vivo.The results have shown that *Diospyros lotus L*. fruits extract has antioxidant activity that may protect against hemolytic damage induced by Vicia faba bean extract in both G6PD-deficient human and rat erythrocytes. The study gives a scientific basis for the efficacy of the fruit extract as used in Iran. The fact that this was shown in human erythrocytes in vitro is significant and provides a rationale for further testing in vivo in G6PD-deficient human populations (Azadbakht et al., 2011).

Tea extracts

Tea extracts are known to terminate inflammatory conditions, and its usage has been reported to prevent skin damage caused by UV irradiation (Vayalil et al., 2004). There are three types of tea: black, Oolong, and green tea. Green tea is widely consumed in Japan, China, and other Asian nations and is becoming more popular in Western nations. The difference between green tea and the others is that green tea is not fermented, thus preventing antioxidants from being lost during that process. Therefore, and in contrast to black tea, green tea contains high concentrations of polyphenols such as epigallocatechin-gallate (EGCG). Tea polyphenols have been shown to inhibit proteasome function, thereby terminating inflammation (Nam et al., 2001). Ko et al investigated the pro-oxidative effects of tea and some polyphenols (epigallocatechin-3-gallate and epigallocatechin) on G6PD-deficient erythrocytes in vitro. The tea extracts significantly decreased the level of reduced glutathione in G6PD-deficient erythrocytes in a dose-dependent manner but did not alter the level in normal erythrocytes. The authors believed it is highly unlikely the plasma concentration of these compounds would reach a harmful level in individuals with G6PD deficiency under conditions of normal consumption. Instead, they suggested that an additive effect might occur if individuals with G6PD deficiency take additional oxidative drugs. No case reports in the literature have described hemolysis when individuals with G6PD deficiency consumed tea and/or polyphenols, and, to date, involvement of tea and some polyphenols in hemolysis in individuals with G6PD deficiency has not been confirmed in vivo (Ko et al., 2006).

Fenugreek seeds

Fenugreek (Trigonella foenum graecum) is a plant that belongs to the Leguminosae family (Kaviarasan et al, 2006). It is established that *fenugreek* seed extract has anti-diabetic effects through several pathways, such as restoring pancreatic β cell function and inhibiting sucrase and alpha-amylase activities (Baquer et al., 2011). It is full of 4-hydroxyisoleucine, which directly induces insulin secretion from pancreatic β cells (Kaviarasan et al, 2006).. Furthermore, there are some evidences that its seed extract reduces serum triglycerides, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) (Baquer et al., 2011). Beside these properties, some anti-inflammatory and anti-nociceptive actions were also attributed to its seed extract (Kawabata et al., 2011). In one case report, *fenugreek* seeds were suspected to have triggered hemolysis in a an individual with G6PD deficiency. Acute hepatitis and a1-antitrypsin deficiency were excluded as causes of hemolysis, but neither the diet nor possible exposure to drugs in this patient, who had an 8-month history of poorly controlled diabetes, was investigated, and therefore a causative relationship between

fenugreek and hemolysis could not be demonstrated conclusively (Sadler et al., 2009).

Henna (*Lawsonia inermis*)

Henna is a dye derived from the dried leaves of the flowering plant Lawsonia inermis (Raupp et al., 2001). The dye principally contains 2-hydroxy-1, 4-napthoquinone, but also flavonoids and steroids. Henna continues to be widely used in Africa, Asia and the Middle East, to colour or adorn the skin, nails and hair. Its use is often associated with religio-cultural events, including marriage. Reports of haemolysis with the topical use of henna have been reported (Kandil et al., 1996; Kok et al., 2004; Zinkham et al, 1996; Seyedzadeh et al., 2007; Katar et al., 2007). Raupp et al. presented four cases of G6PD deficient individuals who experienced haemolytic crisis following topical henna application. Acute renal failure occurred in one case and the patient died after 2 days of admission (Kandil et al., 1996). In another study by Kandil and colleagues, the authors reported (Kok et al., 2004), G6PD deficient individuals who were admitted due to acute haemolysis after 24–72 h post-henna application. Other authors have also reported similar features after application of henna. Taken together, existing data reviewed showed that henna could increase the risk of haemolysis in infants and children with G6PD deficiency (Kok et al., 2004).

Gingko biloba

Gingko biloba is the fourth most frequently used source of herbal medicine in the United States, accounting for 4.3% of all single herb sales in 2001. Its extract is used for many clinical conditions, including dementia, mild cognitive impairment, cerebrovascular and arterial insufficiency, tinnitus, vertigo, asthma, and allergies (Bent et al., 2005). Increasing evidence suggests that *G. biloba* leaf extract can act as a prooxidant in vitro and in vivo. These extracts contain quercetin (Pawlikowska-Pawlega et al., 2003) and procyanidins (Robaszkiewicz et al., 2007), which induce oxidative stress, especially in high doses. *Gingko* is generally well tolerated, but can increase the risk of bleeding if used combination with warfarin, antiplatelet agents or in subjects with G6PD deficiency. One case report discussed a 55-year-old woman with a history of hypertension and dementia, who was given a 17.5 mg injection of *Gingko biloba* leaf extract to improve her memory and subsequently developed jaundice. Cessation of therapy improved her condition and she was discharged 5 days later. Taking into consideration the widespread use of this supplement and paucity of reports, it is highly improbable that *Gingko* can lead to haemolysis in G6PD deficiency (Lai et al., 2013).

Acalypha indica

Acalypha indica is a weed found in various parts of Asia, and widely used in Ayurveda for its claimed anti-inflammatory, antimicrobial and antitussive effects (Seebaluck et al., 2015). Sellahewa first described *Acalypha indica* induced haemolysis in four patients in Sri Lanka (Sellahewa, 1992). Since then, three other studies have similar reported incidences of acute haemolysis after ingestion of *Acalypha indica* (Narasimhan et al., 2014; Lamabadusuriya and Jayantha., 1994; Senanayake and Sanmuganathan., 1996). In all cases, the authors suggested that consumption of a broth containing *Acalypha indica* was the cause of haemolysis. Nevertheless, the actual dose and purity of these extracts were not reported. Indeed, toxicity studies from laboratory studies using low to very high doses of *Acalypha indica* extract in rats found it to be non-toxic to major organs. In view of these contradictory findings, we suggest caution in the consumption of *Acalypha indica* (Sathya et al., 2012; Lee et al., 2017).

Conclusion

In summary, herbal medicines play an important role in the general health-care system of many developing countries worldwide and are gaining popularity rapidly in many developed countries. Most individuals with G6PD deficiency are asymptomatic, with no clinical manifestations of illness and the unaware use of herbal medicines may have dangerous consequences.By examining herbal medicines in this review article, it can be seen that G6PD deficient patients should use herbal medicines cautiously because some of them, like henna, have been proven to cause hemolytic, but on the other hand, some plants can be used to Reducing the dangerous effects of this disease but more research is needed.

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