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HISTORICAL CASE REPORT

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A 12th Century Report of an Adverse Effect of Henna in Iranian Traditional Medicine: Topical Use May Cause Hyperbilirubinemia

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ABSTRACT

Henna or *Lawsonia inermis L.* is a plant used for medicinal and cosmetic purposes worldwide. Lawsone is an important chemical ingredient of henna leaves with an oxidizing effect that can cause acute haemolysis in vulnerable individuals including G6PD deficient patients. One of the symptoms of haemolysis is red discoloration of urine. It is thought that this effect of henna has been discovered by modern medicine but there are earlier reports in history of medicine. In fact, investigating traditional medicine books shows that urine color change due to topical use of henna has been mentioned by Aghili Khorasani who is a famous scholar of Iranian Traditional Medicine in the 12th century.

In parts of world where unexplained cases of hyperbilirubinemia and G6PD deficiency are more frequent, cutaneous application of henna has the potential to initiate oxidative haemolysis, which may present as red discoloration of urine. Since henna is widely used in different joyful events and also as a home remedy for minor problems, this effect should be considered..

Keywords: *Lawsonia alba*, Iranian Traditional Medicine, haemolysis, Mohammad Hossein Aghili Alavi Khorasani Shirazi, hyperbilirubinemia

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Introduction

Lawsonia inermis L. (*Lawsonia alba*), commonly referred to as henna is a plant used worldwide for medicinal and cosmetic purposes. The natural habitat of this plant belonging to the Lythraceae family, is mentioned to be eastern tropical and subtropical Africa, and southern Asia (1). Polatschek and Rechinger doubt whether henna is indigenous to southern Persia but according to Dr. Ghahreman, henna is cultivated in some southern regions of Iran, namely Baluchistan, Bam and Narmashir (2).

Use of henna by man dates back to pre-dynastic Egypt, where it was used to disguise the appearance of aging and hair greying (3). The earliest artefact depicting women with henna stains on the soles of their feet, nails and hands is a wall in Akrotiri, "The House of the Ladies," on the Aegean island of Thera (Santorini, southeast of Greece's mainland) c. 17th century BCE. In this wall painting, both women have henna stains on their soles and fingernails (4). Nowadays, in some countries especially Africa, Asia and the Middle East henna is traditionally applied on skin in some ceremonies including marriage, birth of a child, and etc. Its pulverized leaves -when soaked in water- produce a russet or reddish-brown dye that is used for coloring hair, skin, and fingernails as well as fabrics including wool, silk and leather. This plant has several medicinal properties such as fungicidal, anti-inflammatory and analgesic effects. Henna is also used by some people as a household remedy for minor ailments like combat lice and dandruff, diabetic foot disorders and ulcers, curing ring worm and acceleration of wound healing (3).

An important chemical ingredient responsible for the color of henna leaves, is Lawsone (2-hydroxy-1,4 naphthoquinone), which is chemically similar to 1,4 naphtoquinone, a metabolite of naphthalene. This chemical substance may cause haemolysis in G6PD deficient RBCs. An important X-linked disease and the most common human enzyme defect (5), G6PD deficiency affects 359.19 million cases, 4.87% of the worldwide population and causes 16,743 deaths per year; 0.03% of global deaths (6). This hereditary genetic defect is due to mutations in the G6PD gene, resulting in functional variants with many different biochemical and clinical phenotypes. The most frequent clinical manifestations of G6PD deficiency include neonatal jaundice, and acute haemolytic anaemia, usually triggered by exogenous agents (5) such as infections, medications, nutriments or different oxidising agents. Zinkham and Oski have investigated oxidising effect of Lawsone in vitro and concluded that it is capable of inducing oxidative haemolysis (7). There are also case reports of this effect of henna in children of different parts of the world.

Objectives

The aim of this study is to analyse the first report of henna topical application side effect by Mohammad Hossein Aghili Alavi Khorasani Shirazi from the 12th century.

Materials and Methods

It is thought that the oxidizing effect of henna is first reported in modern pharmaceutical books such as ***Martindale: The Complete Drug Reference*** (8). However, more research shows that earlier reports about this side effect can be found in

books of Iranian Traditional Medicine.

Mohammad Hossein Aghili Alavi Khorasani Shirazi (known as Aghili) is a prominent Iranain physician of the late 12th and early 13th century. He is from a dynasty with many physicians and scholars who have made important contributions to Iranian medicine from the Safavid to the early Qajar period (9). Aghili's life history is not clearly known but it seems that he was born in Shiraz. Some of his books have remained including *Kholasat-al-Hekmah* (about principles of Iranian medicine), *Mo'alejaat* (about disorders and their treatments), *Makhzan-al-Advieh* (about monotherapy with either herbal, animal or mineral drug monographs), and *Ghrabadin-e Kabir* (about combination therapy) which are written in Persian(10). *Kholasat-al-Hekmah* is written in 1195 and explains theoretical and practical medicine thoroughly. In this book, Aghili mentions his personal scientific and independent opinions while examining the viewpoints of scholars who lived before him.

In the first volume of this book, Aghili mentions different notes about urine characteristics and different conditions pertaining to it. Here he writes: "applying Henna to skin, hands and feet gives a reddish color to urine especially if used for a long period and in people who are *Nazok-badan* and *Raghigh-ol-jeld*". It is evident from this sentence that Aghili knew side effect of henna heppened in a just a special group of people who used this plant and not everybody. Also, it seems that by "*Nazok-badan and Raghigh-ol-jeld*" he means susceptible groups which could be children and very thin adults. This is also approved by modern medicine. Thus far, the reports of haemolysis due to henna, have all been in G6PD patients and also children. In 2004, McMillan et al (11) concluded that lawsone is a weak direct-acting haemolytic agent and extra-erythrocytic metabolism is not needed for it to induce hemotoxicity. So, the haemolytic response to henna may be restricted to patients with compromised antioxidant defences.

As we understand from the text, it is clearly mentioned that henna may discolour the urine. About the word "reddish" here, we know that when Iranian Traditional Medicine scholars mention the name of a color, they mean a range to which that color belongs and not just that specific color (12). The same is true here about red and its range of colors including dark red, reddish brown, etc.

Aghili continues his words by mentioning a note about urine opacity: "but it is *ghalil-ol-eshragh*". In the words of modern medicine, this sentence means that urine is clear. According to modern medicine, Red colour of the urine can be caused by presence of erythrocytes, haemoglobin and myoglobin. Urine opacity may be the result of presence of these factors in urine: erythrocytes, leukocytes, epithelium, bacteria, fat drops, salts precipitation (urates, phosphates, oxalates); and also as a result of pH and temperature of urine storage (low temperature leads to salts precipitation) (13). Thus, because of lack of these factors in haemolysis, the red urine in haemolysis is clear.

Discussion

Lawson, an important part of henna leaves, can cause haemolysis and this is what Aghili, who is a well-known ITM scholar, mentioned in the 12th century. Literature review shows that there were medical reports of adverse reactions even as serious as death and near-death experiences in some children to whom henna was largely applied. Reports are from the countries in which henna is usually used traditionally in events of joy and happiness.

In 1992, Hashim et al. (14) wrote about 31 cases -in five years- with lawsonia alba intoxication from Sudan. They had used a mixture of hen-

na and a chemical dye para-phenylenediamine (PPD) to accelerate the dying process. While all of these cases developed severe angioneurotic oedema, acute renal failure and dark urine occurred in five cases. 13 patients died within one day of symptom presentation. Şık et al (15) reported a 9-year-old Turkish girl with psoriasis who developed multiple organ failure due to applying a mixture of black henna and PPD on her skin. The symptoms started after one hour of topical use of the mixture and included intravascular haemolysis, rhabdomyolysis, acute renal failure, upper respiratory and muscle edema, and cardiac arrhythmia. These symptoms may be suggestive of PPD poisoning and are not related to use of henna alone. The patient died on day four. There is no information on the G6PD status of the patient.

In 1996, Kandil et al. (16) wrote a report of their 10-year experience in Kuwait on 15 G6PD deficient baby boys who developed haemolysis and hyperbilirubinaemia a few days after henna application over their bodies. Katar et al. (17) reported jaundice and pallor in a Turkish seven-day-old boy to whom henna was applied for prevention of nappy rash and for traditional cosmetic purposes. Symptoms occurred after 29 hours of using henna. In 2001, Raupp et al (18) reported four cases from United Arab Emirates who had haemolysis following henna application. Case 1 was a G6PD-deficient term baby girl who developed lethargy and jaundice 24 hours after henna application all over her body. She was 20-days old and recovered after two exchange transfusions. that the second case reported by Raup et al, was a G6PD deficient two-month-old boy who had jaundice, pallor and red-colored urine 48 hours after application of henna to his palms and soles. After two more days, he was brought to hospital in a shock state. His urine culture was sterile. Despite transfusion, he died two days after hospital admission. Raup´s third case was a G6PD deficient boy who was 3 years old and henna was applied on his soles. After three days, he was jaundiced and after one more day passed, he developed increasing pallor. He survived after transfusion. The fourth case Raup described was is a four- year-old G6PD deficient girl who showed haemolysis syndromes including jaundice, pallor and dark-colored urine within 2 days of henna application to her palms and soles. She recovered after one week.

Devecioğlu et al (19) reported a 27-day-old Turkish boy who was G6PD deficient and had jaundice, pallor and dark urine in the fourth day of henna application on his belly and legs for treating diaper rash. The infant didn´t survive. Ramiar and Kalantari (20) in 2005 reported an Iranian 7-year old boy who developed altered level of consciousness, jaundice, pallor and haemoglobinuria 24 hours after applying a herbal combination of henna, coconut oil and Licorice on his skin because of vesiculobullous lesions. He received transfusion and survived.

In 2007, Seyedzadeh et al (21) reported an Iranian 42-day old G6PD deficient boy who had haemolysis after henna was applied due to napkin dermatitis. He recovered 3 days after transfusion. Kheir et al (22) reported a Sudanese G6PD deficient boy to whom Henna was applied topically in the joyful event of kindergarten graduation ceremony, 3 days before hospital admission. He had tea- like urine, yellow sclera, jaundice and a short systolic murmur on the left sternal border. After transfusion, he recovered fully. He had a history of similar symptoms when he was 2 years old and henna was applied to his skin on the occasion of his circumcision. He was not taken to hospital previously. In 2018, Alhazmi et al. (23) reported a 4-month old Arabian girl who

had symptoms of haemolysis 3 days after topical application of henna to her body. She was found to be G6PD deficient in lab tests. Her mother had a similar history on the event of henna application in her wedding but it was left unnoticed. The baby recovered after transfusion.

However, this side effect of henna is not confined to small children and has been reported in the elderly as wel. Kök et al wrote in 2004 about siblings who had henna applied over all their bodies from throat to soles for improving symptoms of ichthyosis vulgaris. One of the siblings was an 11-year old boy and the other was a 7-year old girl. Both were G6PD deficient and became pale and passed red and low urine 6 hours after henna application. The girl died 2 days after transfusion but the boy remained alive (24). Another report of haemolysis is written by Soker et al (25) in 2000. It is about an 11-year-old boy who was G6PD deficient and had henna applied all over his body due to psoriatic skin lesions. After one day, he presented jaundice, pallor and reddish urine. He survived after transfusion.

Conclusion

Lawsone which is a chemical substance in henna leaves, is an ingredient that can cause oxidative injury to RBCs. In parts of the world where there is unexplained hyperbilirubinemia and G6PD deficiency is more frequent, cutaneous application of henna has the potential to initiate oxidative haemolysis. One of the symptoms of this event is change of urine color into red. Aghili Khorasani is one of great scholars of Iranian Traditional Medicine that has recorded this event in his book, *Khulasat-al-hekmeh* in the 12th century many years before modern medicine have declared.

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