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Unlocking The Potential Of Hemoglobin Enhancement Agents: A Comprehensive Review

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Abstract

Hemoglobin is an important protein found in red blood cells and is responsible for the two-way respiratory carrier, transporting oxygen from the lungs to the tissues and facilitating the return transport of carbon dioxide in the body. The development of hemoglobin enhancers is an area of medical research interest aimed at improving oxygen delivery and potentially treating various health conditions. This review aims to explore the role of hemoglobin activators, their mechanism of action, current applications, and potential benefits. Mostly beetroot, dates and findla are mainly consumed as food additives for hemoglobin. And to help increase hemoglobin.

Keywords: Hemoglobin, Haemoglobin enhancer, Beetroot, Dates and Findla.

INTRODUCTION:

Transport oxygen from the environment into cells and transport Carbon dioxide and H+ are produced in the opposite direction of metabolism which is essential for the survival of vertebrates. The reversible binding of the ligands to the hemoglobin molecule and the proper allosteric interactions between the binding sites considerably boost the carrying capacity of O2, CO2, and H+ in blood. All vertebrates, with the noteworthy exception of Antarctic icefishes, contain Hh, which significantly reduces the circulatory demand[1].
One of the proteins that has been researched the most, hemoglobin, has led to a thorough knowledge of the links between its structure and function. Since its structure and activities are well understood, Hh has earned the moniker "honorary enzyme" and serves as a useful model for research on allosteric interactions in other proteins[1]. Fish Hbs in particular have been the subject of extensive research on vertebrate Hbs, which has continued to disclose fascinating new facets of cellular and molecular regulatory mechanisms. Since fish Hbs were last examined in this book series, significant advancements have been made[2]. The goal of this chapter is to provide a summary of what is currently known about the molecular structure, conformational variations, allosteric connections, and the many activities of fish Hb.
Red blood cells contain a metalloprotein called hemoglobin (Hb). Oxygen is circulated throughout the body via red blood cells. Hemoglobin serves as the oxygen transporter in the red blood cells of all vertebrates[3]. Iron is present in hemoglobin, which makes up 96% of the dry weight of a red blood cell. Hemoglobin is a component of every human body. The hemoglobin level is measured in grams (gm) per deciliter (dL) of whole blood. An adult guy with normal hemoglobin levels ranges from 13.8 to 17.2 g/dL. Adult females (non pregnant) should have 12.1–15.1 g/dL of hemoglobin[3]. The oxygen equilibrium curve (OEC), which displays Hb's oxygen saturation (SO2) at various partial pressures of oxygen (pO2), serves as evidence that Hb's principal job is to transfer oxygen (O2) from the lung to tissues by cooperatively binding and releasing

oxygen[4]. The Oxygen affinity for Hb is measured by the partial pressure of oxygen (pO2) at 50% oxygen saturation (SO2), which is approximately 26 mmHg for normal adult human Hb (HbA)[4].
Two classical states' equilibrium have been used to describe the Hb function: the relaxed (R) state (liganded Hb), which has a high affinity for Oxygen, and the tense (T) state (unliganded Hb), which has a low affinity for Oxygen, provide a structural foundation for cooperative effects that make Oxygen absorption and release in vivo more efficient[5,6,7].

STRUCTURE OF HEMOGLOBIN:

Hemoglobin comprises four subunits, each having one globulin chain (polypeptide chain) and one heme group[8]. Each globulin chain includes an essential iron-containing porphyrin molecule called heme. An iron atom contained within the heme molecule is essential for carrying oxygen and carbon dioxide in human blood. The iron in hemoglobin is also responsible for the red color of blood[8]. Hemoglobin is made up of four protein molecules (globulin chains) that are linked together; Two alpha-globulin chains. Two beta-globulin chains(Fig. 1)[8,9]. Similar in length but with different amino acid sequences are the alpha and beta chains. Human hemoglobins, whether they are adult or embryonic, all have the same alpha chain. The gamma chain of fetal hemoglobin (α2γ2), the beta chain of adult-normal hemoglobin (α2β2), and the delta chain of HbA2 are among the non-alpha chains[9].

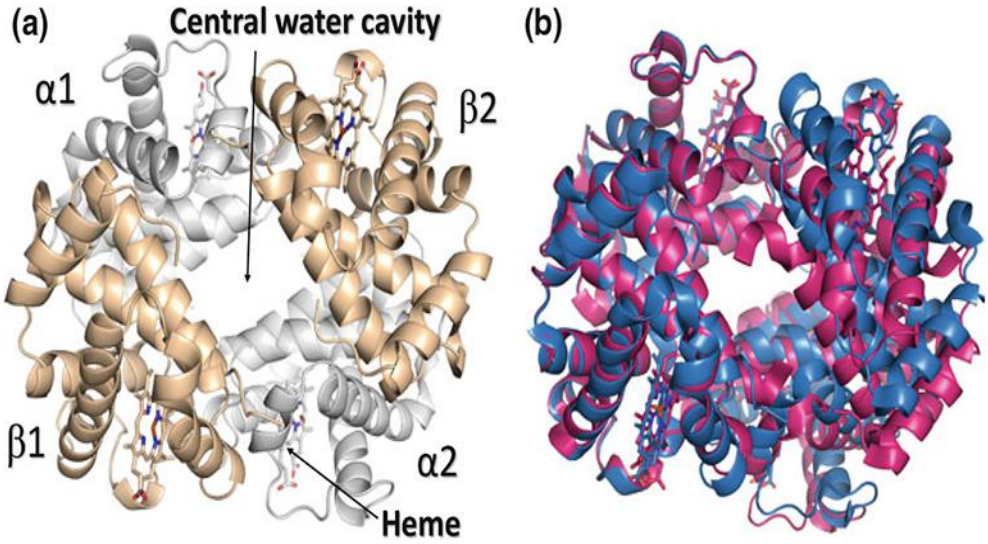

Fig.1: Crystal structure of hemoglobin. a Overall quaternary structure of Hb with the two α chains and β chains colored grey and tan, respectively. b Structure of oxygenated (R state) Hb (magenta) superimposed on the structure of deoxygenated (T state) Hb (blue). Note the larger central water cavity in the T structure.

The two sites of entrance into the central water cavity that are greater in T state structure than R state structure are the α-and β-clefts. More salt-bridge/hydrogen-bond interactions than R state structure are also present at the interdimer interface (α1β1–α2β2) of the T state structure[9]. The 7 and 8 helices, referred to respectively as A-H, that make up the α-subunits and β-subunits are connected by non-helical segments. The E and F helices of each subunit provide a binding pocket for heme. The four nitrogen atoms of the porphyrin ring work together to coordinate the ferrous ion stored in the middle to form the heme. an imidazole of a histidine residue found on the F helix (proximal histidine or His (F8)), the Fe is further covalently bound to Hb at the heme proximal pocket[10].
Through hydrogen-bond interaction, a histidine residue (His E7) in the distal pocket stabilizes the attached Oxygen. A very weakly bound water molecule fills the α-cleft of deoxygenated hemoglobin, leaving a warped octahedron in its place[10]. central water cavity, Allostery is a result of cooperativity events that impact the T → R transition and are sparked by α- and β-clefts, as well as salt-bridge/hydrogen-bond interactions across the α1β1–α2β2 (α1β2 or α2β1 or α1α2 or β1β2) dimer interface[11,12].

Some Fruits help to increase hemoglobin levels:

Beetroot:

Beta vulgaris, a member of the Chenopodiaceae family and a well-known plant, is commonly known as beetroot[13,14]. Beetroot is well-known for its therapeutic benefits and usefulness as a juice. In the past, beetroot was used as an aphrodisiac and to increase the hormones involved in sexual activity. To remove kidney and bladder stones, beetroot juice is utilized as a natural therapy[14,15]. Beetroot has received a lot of attention as a meal that promotes good health[16,17].Beetroot is cultivated in several nations across the world, widely consumed as part of the standard diet, and frequently utilized in food manufacture as a food coloring ingredient[18,19].

Beetroot nutrient include folate – a vitamin that helps keep your biood vessels healthy and Potassium to help protect your Heart[20].

Beets are also an excellent source of:

- **Folate**
- **Manganese**
- **Vitamin C**
- **Vitamin A**
- **Potassium**

Ascorbic acid, carotenoids, phenolic acids, and flavonoids are among the many phytochemical components found in beetroot[21,22]. The group of extremely bioactive pigments known as betalains is found in only a few crops, including beetroot. It is classified as either betacyanin pigments, which are red-violet, or other members of the betalain family[23,24]. Beets contain nitrate in addition to flavonoids, anthocyanins, and betaine, all of which have cardioprotective properties[25,26]. The plant B. vulgaris is a high source of betaine, which has physiological benefits include lowering plasma homocysteine levels, shielding the liver from toxins, and modifying the kidneys' osmolyte function[27]. Beetroot is a rich and nutritious source, and it has health-promoting properties such as antioxidant and anti-inflammatory properties and hemoglobin boosters[28].Beetroots were primarily dietary sources of nitrates, May have important implications for managing cardiovascular health[29].

Antioxidant:

Recently, antioxidants of the class of betalain pigments were identified. Due to its phenolic components, beetroot has been shown in several published research investigations to possess high antioxidant effects[30]. betalains and a significant amount of superoxide, hydroxyl anion, and superoxide radical scavenging action towards stable DPPH. Beet root pomace, a byproduct of the juice industry that is inedible yet likely a significant source of antioxidants, is a waste product from beet root harvesting[31].

Anti-inflammatory activity:

A rat model of paw oedema caused by carageenan was used to test the beta vulgaris plant's anti-inflammatory effects. A 1000 mg/kg dosage of an aqueous extract from the plant's leaves significantly reduced the paw oedema. Beta vulgaris exhibited anti-inflammatory activity in response to foreign body-induced inflammation[32,33].

Anti-hypertensive:

Heart disease is largely brought on by high blood pressure, a widespread public health issue. According to recent studies, consuming beetroot in bread goods or as a supplement to juice lowers both systolic and diastolic blood pressure. It has been more than 30 years since research on red beet juice's ability to lower blood pressure and enhance the physiological response to exercise was published[34,35,36].

Dates:

The largest agricultural crop is the date palm (Phoenix dactylifera), which is widely distributed across the Arabian Gulf region, including Saudi Arabia, Northern Africa, Pakistan, India, and the United States (California)[37]. Dates are mostly composed of carbohydrates, which may make about 70% of the total weight (primarily the sugars sucrose, glucose, and fructose). In addition to being a wonderful source of fiber, dates also provide a lot of essential vitamins and minerals, including sizeable levels of calcium, iron, fluorine, and selenium[38,39,40]. The fruits, bark, and leaves of the date palm are the portions, and they have a wide range of industrial and medical uses. When mature, date fruits have a sugar content ranging from 72 to 88%, making

them a high-energy food source[41]. Date fruit is rich in phytochemicals such as carotenoids, polyphenols (e.g., phenolic acids, isoflavons, lignans, and flavonoids), tannins, and sterols[42]. In this way, they are responsible for their antioxidant and antibacterial activities, anti-inflammatory properties, and other health benefits like haemoglobin[43].

(a) **(b)**

Figure 1. (a) Date palm tree and (b) Date fruit

Carotenoids:

The lipid components of the date fruit include carotenoids, which are regarded as a significant family of phytonutrients. They serve as precursors of vitamin A, which is essential for eyesight and acts as an antioxidant to shield cells from the harmful effects of free radicals[44]. Dates include lutein, β-carotene, zeaxanthin, and neoxanthin as their main carotenoids. In comparison to red-colored date variations, the yellow color date variety had greater total carotenoids. According to reports, the yellow fruits also contain a complex blend of carotenol fatty acid esters[45].

Phenolic Acids:

Phenolic acids, which include an aromatic benzene ring with an attached hydroxyl function and one or more carboxylic acid groups, are among the major secondary aromatic plant metabolites. Dates contain a significant amount of phenolic acids, according to several study organizations[46,47]. Phenolic acids, which are mostly found in the bound form, may be found in a variety of dates in varying amounts and patterns. Fresh dates had an average total phenolic level of 193.7 mg/100 g, whereas dried dates had a total phenolic value of 239.5 mg/100 g[48].

Phytosterols and Phytoestrogens:

In the lipid-soluble portion of the date fruit, phytosterols are yet another important phytochemical. With chemical structures that are comparable to those of cholesterol, these molecules are only found in plants[49]. Phytoestrogens are organic substances that have the ability to bind to estrogen receptors and have a variety of estrogenic or antiestrogenic effects[50].

Findla (Prickly Pears):

Opuntia ficus-indica (L.) Mill., sometimes known as the prickly pear or nopal cactus, is a member of the dicotyledonous angiosperm Cactaceae family. A tropical and subtropical plant is O. ficus indica[51]. Locally it is called as nagphani or danda thohar. It has different names in India like Hathlo thor, chorhthlo (Gujarati), Haththathoira, Nagphana, Nagphani (Hindi), Snuhi, Vajrakantaka, Bahushala (Sanskrit), Nagadali, Nagakkali, Chapati balli (Tamil), Nagamulla, Nagajemudu (Telugu), Nagphani, Thuar (Urdu)[52]. The nutritional makeup of foods is frequently utilized for nutritional education, assessing the effects of food choices on public health, assessing dietary consumption, and creating and implementing specific recommendations for eating

behaviors[53]. D-glucose, D-galactose, L-arabinose, D-xylose, L-rhamnose, as well as D-galacturonic and glucuronic acids, are all present in plant mucilage[54]. Findla has many uses, such as anti-aging, anti-inflammatory, brightening skin tone, and making skin smoother. It is also helpful in healing cuts, wounds, blemishes, and reducing dark circles[55].

Figure 2. Findla (Prickly pear) fruits.

Conclusion:

Overview of the molecular structure of Hb, relating to its primary function of oxygen transport. Beetroot, dates, and Findla have the ability to improve the carrying of oxygen and carbon dioxide in human blood and also help in the enhancement of hemoglobin. Hemoglobin gives red color to blood. It is provided with folate, vitamins, and minerals. It is a functional food with huge health benefits: antioxidant, anti-inflammatory, anti-hypertensive, and other chronic metabolomics activity. Beetroot, which has been primarily a source of dietary nitrate, may have important implications for managing cardiovascular health. In these cells, hemoglobin performs the dual roles of an antioxidant and a regulator of iron metabolism. Hemoglobin's affinity for oxygen, which can be used to treat disorders brought on by hypoxia and ischemia as well as sickle cell disease.

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