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Role of medicinal plants in free radical induced sickle cell anemia

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Abstract

Sickle cell disease (SCD) is a common recessively inherited disorder of hemoglobin affecting peoples everywhere in the world. The homozygous state (SS) is associated with complications and reduced life anticipation. The symptoms including, shortness of breath, heart palpitations, abdominal pains, aches and pains in the muscle. One cause of this disease is oxidative stress which is an imbalance between the reactive oxygen species and the potential of the body to neutralize these reactive species. An anti-oxidant is a substance which prevents oxidative stress by scavenging the free radicals. Medicinal plants are good and rich sources of natural antioxidants. Crude extracts from plants have been used in treating many diseases since ancient times. Various advances in scientific research on the use of plants and herbs explore the beneficial aspects of traditional medicine. This review highlights the role of oxidative stress in the progression and development of Sickle Cell Disease (SCD) and reviews the available literature reporting antisickling properties of a number of plants extracts.

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Introduction

Sickle-cell disease (SCD), or sickle-cell anaemia or drepanocytosis, is an autosomal recessive genetic disease, characterized by red blood cells that acquire rigid, sickle shape. It decreases the cells' elasticity and results in various complications. Mutation in the hemoglobin gene leads to this disease. It reduced life expectancy. Sickle-cell disease is common in people of those areas where malaria is or was common. This is a specific form of sickle-cell disease in which there is homozygosity for the mutation that causes HbS. It is also termed as "HbSS", "SS disease", "haemoglobin S" or permutations thereof. , in heterozygous people the individual has only one copy of the mutated HbS and one copy of another abnormal hemoglobin allele. In them some forms of this disease are "HbAS" or "sickle cell trait". Sickle-haemoglobin C disease (HbSC), sickle beta-plus-thalassaemia (HbS/β+) and sickle beta-zero-thalassaemia (Plat et al., 1994). Sickle cell disorder is a haemoglobinopathy caused by a point mutation in the globin gene (Ingram, 1956). The clinical severity varies widely from the milder sickle cell trait (heterozygous) to sickle cell anemia (homozygous) (Wang, 2004). Because of mutation the red blood cells (RBCs) undergoes polymerization converting into characteristic irreversible sickled cells.3 This disorder is the commonest inheritable disease associated with haemoglobin most common in Africa and Southeast Asia (Wang, 2004) and (Agarwal, 1980). In India, it affects people in the central and southern parts 4 in central India the disease have a higher prevalence than in the rest of India (Agarwal, 2005).

Oxidative stress and sickle cell anemia

Anemia is one of the major health problems. According to the World Health Organization, about 30 percent of people throughout the world suffer from anemia. Iron deficiency is the most common cause of anemia; however, reactive oxygen species (ROS) has a great potential to cause anemia. ROS in erythrocytes occur either by activation of ROS generation which cause suppression of anti-oxidative/redox system. When erythrocytes experience an excessive elevation of ROS, oxidative stress develops. ROS are considered to play a crucial role in the pathogenesis of many disorders of erythrocytes, such as sickle cell anemia, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Deficiency of antioxidant enzymes such as superoxide dismutase 1 (SOD1) Develop oxidative stress in erythrocytes and causes anemia, some transcription factors such as p45NF-E2 or Nrf2 are also the causative agents of anemia (Wellems *et al.,* 2009).

Cellular oxidative stress and anti-oxidative system

Under normal physiological conditions antioxidant defense system, balance the ROS and prevents or limits oxidative damage. Intracellular metabolism is the generator of ROS such as superoxide (.O2-), hydrogen peroxide (H_2O_2), and hydroxyl radical (.OH)., oxidative stress occur due to imbalance between oxidants and antioxidants because of Increased pro-oxidants and/or decreased antioxidants trigger a cascade of oxidative reactions. Oxidative stress can damage specific molecular targets (lipids, proteins, nucleotides, etc), resulting in cell dysfunction and/or death. Cytochrome P450 nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, nitric oxide synthase (NOS), xanthine oxidase (XO), and lipoxygenase are the enzymes which responsible for ROS generation. While enzymatic complexes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), peroxiredoxin (Prx) act as antioxidant. Some non-enzymatic systems such as flavonoids, carotenoids, ubiquinols, reduced glutathione (GSH), uric acid, vitamins C and E also fight ROS (Malowany *et al.,* 2011).

Erythrocyte membrane oxidation by ROS

When the oxygen of the oxy-hemoglobin (oxy-Hb) takes one electron from iron and ferric-superoxide anion complex is formed. During deoxygenation when oxygen is released, the shared electron is normally returned to the iron. If the electrons remain and transfer to oxygen then superoxide anions is formed leaving the iron in ferric state, as a result Hb

is transformed into methemoglobin (met-Hb). Met hemoglobin (met-Hb) is not only produced by the autoxidation of Hb but also by some endogenous oxidants, such as nitric oxide (NO), H_2O_2, and hydroxyl radicals. The resulting met-Hb is unable to bind oxygen, leading to the formation of harmful hemichromes (Rice-Evans and Baysal, 1987). Under normal conditions, spontaneous interconversion of met-Hb and Hb are in balance However, in pathological conditions, increased oxidative stress will increase the production of met- Hb and ROS generation. As the amount of met-Hb Production increases by ROS, Hemichrome formations will also accelerated. The reduction of ferri-hemichrome to ferri-hemichrome causes decomposition of H_2O_2 to hydroxyl radical in the Fenton reaction. Hydroxyl radical is highly reactive that attack on various biomolecules such DNA, proteins and lipids of the members etc. Peroxidation of membrane lipids produced secondary lipid peroxidation products such as malondialdehyde which can damage membrane structure, alter water permeability and decrease cell deformability. The disruption of membrane phospholipids exposes phosphatidylserine (PS) on the outer cell surface. Macrophages recognized these Erythrocytes that have PS exposed on the outer surface engulfed and degrade them (Carrell *et al.,* 1975; Hebbel, 1985; Nur *et al.,* 2011).

Antioxidants are important in free radicals scavenging

Researchers proved experimentally and clinically that antioxidant is crucial in healing and preventing sickle cell disease. Takasu *et al.,* (2004) proved that aged garlic extract have a good effect of on SCD patients. A reduction in the damage to RBC was noted. Green tea has been shown to possessed potent agents who produced 30% reduction in sickling of RBC. Many dietary supplements, such as thiocyanate have been reported to be beneficial in the (Agbai, *et al.,* 1986), management of sickle cell disease. Oxidative stress acivates KCL-cotransport in sickled erythrocytes which make the erythrocytes fragile and dehydrated (Brugnara *et al.*, 2000). Minerals and anti–oxidants are important to be supplied constantly for maintaining hydration and membrane integrity. Many plants constituent have been investigated for their anti-oxidative properties. Vitamin E, a fat-soluble antioxidant, has been identified experimentally as curative agent of anemia in anemia induced animal model. Vitamin E is an essential erythropoietic factor for certain species of animals. Treatment with vitamin E increased the erythropoiesis. Results of some of clinical trials suggested that vitamin E have putative role In the prevention of some types of human anemia by, enhancing Erythropoiesis and provide stability to erythrocyte membrane proteins and lipids. Many clinical trials have shown that antioxidants such as vitamin E improve hemolysis, by longer erythrocyte lifespan; in elevated hemoglobin level (Corash *et al.,* 1980; Hafez *et al.*, 1986) .Treatment with high doses of vitamin E reduces oxidative stress-induced erythrocyte injury (Newman *et al.,* 1979; Johnson *et al.*, 1983).

Phytochemicals with antisickling properties

Due to the lifesaving and therapeutic properties, plants have been used by native people from ancient times (Olagunjua *et al.,* 2009). Herbal medicine is adventitious over synthetic alternatives. In the developing countries nearly 70% world population is dependent on such traditional therapies (Sarkadi *et al.,* 1979; Bewaji *et al.*, 1985). Phytochemicals in the extracts of various plants are capable of treating various diseases. Some of the bioactive components from medicinal plants include: saponins, tannins anthraquinones, flavonoids, glycosides, etc. Some other examples of disease treating components of plants include morphine, atropine, codeine, steroids, lactones and volatile oils. In recent years these bioactive components are used in different forms such as infusions, syrups, concoctions, decoctions, essential oils, ointments and creams Many plants have been investigated invitro and have shown potential to cure SCD. The common examples are Griffonin and Ouabain (Larmie *et al.,* 1991), *Fagara xanthyloides* (Honig 1975 *et al.,* Osoba 1989), *Cajanus cajan* (Akojie 1992; Ekeke 1985; Iwu 1988; Onah 2002) and *Khaya senegalensis* (Fall *et al.*,

1999), in the developing world phytomedicines could be important in the management of SCD, Some of these plants reported are *M. charantia* (Semiz *et al.,* 2007), *Cymbropogon citratus* and *Camellia sinensis*(Ojo, 2006), *Scoparia dulcis* (Adaikpoh *et al.,* 2007), Aged garlic (Ohnishi *et al.,* 2001) and *Picrorhiza kurroa* (Rajaprabhu D). Elekwa *et al.,* (2005) studied that crude aqueous extract of *Zanthoxylum macrophylla* roots possessed anti-sickling properties (Orhue *et al.,* 2005; Orhue *et al.,* 2006) showed that *Scoparia dulcis* can be used to cure sickle cell disease. Twelve plants were screened to possess anti-sickle cell anaemia properties (Mpiana *et al.,* 2007). Some these plants are, *Cymbopogon densiflorus, Ceiba pentandra, Dacryodes edulis, Bridelia ferruginea Caloncoba welwithsii,* and *Vigna unguiculata*. *Khaya senegalensis* contains potents phytochemicals that have antisickling activities (Vanhaelen-Fastre *et al.,* 1999) proved that *Garcinia kola* extracts is more effective in membrane stabilization and used by the locals in Nigeria in the management of sickle cell disease. Phytochemical examination of the roots extract of *Cssus populnea* contained steroidal glycosides and cardiac glycosides and was used for the treatment of inflammation related diseases (Moody *et al., 2003*). *Pterocarpa osun*, *Eugenia caryophyllala* and *Sorghum bicolor* extracts for can be used in the treatment of sickle cell disease (Wambebe *et al.,* 2001). The extract of *Pterocarpus santolinoides* and *Aloe vera* was reported in the management of sickle cell disorder (Ugbor *et al.,* 2006). It has been studied that root extracts of *Fagara zanthoxyloides has anti*-sickling potential (Sofowora *et al.,* 1971). Doses of *Terminalia catappa* are of most impartance in inducing hemolysis of human erythrocytes (Mgbemene *et al.,,* 1999; Hayashi, *et al.*, 1987, Hayashi *et al.,* 1990) studied that *Scoparia dulcis* has a good effect on various diseases.

Conclusion

Oxidative stress is a major cause of anemia and have role in complicating anemia with other infectious diseases. Studies indicate that Antioxidants are most important and vital in lowering or preventing the disease by eradicating oxidative stress.

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