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Antioxidant and Anti-inflammatory Effects of Artichoke or Cynara Scolymus L. as Promising Potential Therapeutic in Anemia

Majid Keramati; MSc [1,2], Vali Musazadeh; MSc [*1,2] & Keyvan Ghadimi; MD [3]

[1] *Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.*
[2] *Student Research Committee, Nutrition Research Center, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.*
[3] *School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.*

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Corresponding author:
mosazadeh.vali05@gmail.com
Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.

Postal code: 5166614711
Tel: +984133340634

ABSTRACT

Artichoke (Cynara scolymus L.) is a perennial plant native to the southern Mediterranean region of North Africa. Today, artichokes are widely grown around the world and buds of artichokes are used as a vegetable all over the world. This plant is widely used in the traditional medicine. Artichoke has antioxidant and anti-inflammatory effects, and countless medicinal properties. Artichoke inhabits reactive oxygen species (ROS) and free radicals due to phenolic acids and flavonoid compounds and also suppresses the activation pathway of NF-κB, thereby could reduce oxidative stresses, inflammatory factors, and prevent suppressing red blood cells probably. It has also been suggested for traditional medicine including blood purification, so it can be used for anemia treatment.

Keywords: *Artichoke; Cynara Scolymus L.; Anemia; Oxidative stress; Inflammatory*

Introduction

Artichoke (Cynara scolymus L.) is a perennial plant which is originated from the southern Mediterranean parts of North Africa. Today, artichokes are widely grown around the world and buds of artichokes are used as a vegetable all over the world (Valladares-Cisneros *et al.*, 2016). Artichoke plays an important role in the preparation of the human nutrition, especially in the Mediterranean region (Negro *et al.*, 2012). In ancient times, it was consumed as a drug in traditional medicine. There is a relationship between improvement of the biliary tract diseases and artichoke and also this plant has been considered as anti-atherosclerosis. In the early of the twentieth century, French scientists began modern research into traditional medicinal and

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used artichoke as herbal medicine. In addition this plant actually stimulate functions of kidneys, liver, gallbladder (Rondanelli *et al.*, 2013), and ROS production (Zapolska-Downar *et al.*, 2002). Artichokes are rich in B vitamins group, especially B1 and vitamin C, and nutrients, such as potassium, magnesium, iron, sodium, manganese, and zinc. The mechanism of artichoke has been studied extensively and has been found to be a rich source of polyphenolic compounds. C.scolymus has been considered as important antioxidant compounds, including cynarin and chlorogenic acid (Jun *et al.*, 2007, Robards, 2003). This biological compound of artichoke leaf extract (ALE) contains high levels of minerals, vitamin C, fibers, polyphenols, flavones, inulin, and hydroxyl cinnamates- caffeoylquinic acid derivatives, as well as a few amount of fat (Ceccarelli *et al.*, 2010, Pandino *et al.*, 2011a, Pandino *et al.*, 2011b). ALE also contains bioactive and flavonoid compounds, such as luteolin glucosides and caffeoylquinic acids. Cynarin is a major dicaffeoylquinic acid and chlorogenic acid is the main monocaffeoylquinic acid. Whereas, luteolin-7-O glucoside is a major flavonoids (Liorach *et al.*, 2002, Wang *et al.*, 2003). Cynarin, chlorogenic acid, caffeic acid, and luteolin are constituents of artichoke leaf extract, contributing to the antioxidant activity of the extract in human neutrophils (Pérez-García *et al.*, 2000) (**Table 1**).

Table 1. Artichoke effects, effective compounds, and the mechanism of action (Sallam *et al.*, 2008).

Effects	Effective compounds	Mechanism
Antioxidant	Luteolin – Chlorogenic acid – Caffeic acid – Cynarin – Luteolin7-O-glucoside	Inhibition of MDA production Reduction of radical-induced hepatocyte killing Inhibition of liver cell damage
Anti-inflammatory	Caffeic acid - Luteolin	Suppress the activating pathway the NF-κB
Inhibiting cholesterol biosynthesis and atherosclerosis	Luteolin	Inhibition of incorporation of (C14)-labelled acetate Reduction of cholesterol and prevention of atherosclerosis
Choleretic	Compound dehydrocholic acid of ALE	Reduction of intrahepatic cholesterol concentration

Antioxidant and anti-inflammatory effects of artichoke

The protective effect of flavonoids against oxidative injury might depend not only on their antioxidant activity, but also depends on their permeability through plasma membranes (Wang *et al.*, 2003). The antioxidant compounds of artichokes has been evaluated in Vitro studies and the antioxidant activity of artichokes was confirmed in numerous clinical studies (Betancor-Fernández *et al.*, 2003, Liorach *et al.*, 2002, Salem *et al.*, 2015, Wang *et al.*, 2003, Zapolska-Downar *et al.*, 2002). A study demonstrated further antioxidant properties, such as chlorogenic acid-, cynarin-, caffeic acid - and lutein with mechanism of inhibiting low density lipoprotein (LDL) oxidation, and C. scolymus leaf extract was an antioxidant acting as a radical scavenger (Pérez-García *et al.*, 2000). However, in vivo studies on rats, the C. scolymus leaf extract has been suggested for reducing lipid peroxidation and protein oxidation, and increasing glutathione peroxidase activity and catalase (CAT) (Ahmadi *et al.*, 2019, Jimenez-Escrig *et al.*, 2003). Artichokes can be significantly protect against sharp rise in malondialdehyde (MDA) and decrease in superoxide dismutase (SOD) and Reduced glutathione (GSH) (Tang *et al.*, 2017). The level of MDA was decreased after the C. scolymus extract administration but the values were not significantly different from the normal control group. Many studies suggested that C. scolymus was anti-inflammator (García-Lafuente *et al.*, 2009, Mahboubi, 2018, Mohamed *et al.*, 2013, Premaratna *et al.*, 2012). C. scolymus suppressed development of inflammation and decreased macrovascular fatty changing specially in the liver

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lobules (Mahboubi, 2018). The high quantity of phenolic and flavonoid compounds of C. scolymus for methanol extract (Pourmorad *et al.*, 2006), made it more effective as an anti-inflammatory in acute inflammation, since flavonoid has anti-inflammatory activities (García-Lafuente *et al.*, 2009). C. scolymus methanol extract significantly reduced the level of IL- 6 and complement C3a (pro-inflammatory of acute inflammation) (Majeed *et al.*, 2015). Artichoke components, such as caffeic acid and its derivatives, and luteolin have suppressed the activating pathway of the NF-κB (Santos *et al.*, 2018). The enzyme of human intracellular AKR1B1 belongs to the aldo-keto reductase superfamily. The AKR1B1-catalyzed reduction of aldehydes, which is part of the intracellular inflammatory pathway, leads to the activation of NF-κB and the expression of pro-inflammatory genes. Low concentrations of the artichok extract inhibited the enzyme AKR1B1. The extract diminished the expression of the inflammation-related enzymes COX-2 and MMP-2, probably by inhibiting the activity of NF-κB (Miláčková *et al.*, 2017).

Anemia

Anemia is a medical condition associated with increasing or decreasing RBCs characterized by the insufficient capacity of oxygen-carrying to meet physiological needs (Marks, 2019). The common cause of anemia is iron deficiency; iron is an integral part of the blood protein and hemoglobin (Hb). Nevertheless, other anemia-related abnormalities include vitamin B12 deficiency, vitamin A, parasitic infections, chronic inflammation, and inherited disorders (Premkumar *et al.*, 2018). Childhood and pregnancy are the most vulnerable groups; about 1.62 billion people are affected by anemia, corresponding to 24.8% of the population all over the world. Anemia is characterized by a decreasing concentration of Hb, the number of RBC or the volume of packaged cells, and impaired function in meeting the demand for oxygen in the tissues. The concentration of Hb in the blood largely depends on physiological characteristics, such as age, sex, and pregnancy status. Other factors that affect the concentration of Hb in the blood are also smoking and environmental factors, such as high altitude areas. Therefore, it is essential to have insights of the various forms of anemia in order to explain better its prevalence and to understand the causes of iron deficiency. Depending on the morphology of the RBC and the cause of the disease, anemia can be classified into several types. Nutrition deficiency anemia (non-haem) results from a deficiency of nutrients and insufficient bioavailability of hemopoietic nutrients, such as iron, vitamin B12, folic acid, and ascorbic acid (Andlid *et al.*, 2018). Megaloblastic anemia is also caused by insufficient folic acid. The inhabitation of DNA synthesis during RBC production makes the cells larger than the normal size (Moll and Davis, 2017). Sickle cell anemia is inherited as an autosomal recessive disease. The sickle-like cells in this anemia block blood that flows to the spleen and cause the spleen to separate (Marks, 2019). Iron deficiency anemia (IDA) is caused by low iron intake from foods or malabsorption of iron in the body, resulting in hypochromic microcytic anemia (Marks, 2019). Due to the parthenogenesis of anemia, it can be concluded that inflammation and oxidative stress can play an important role in causing various types of anemia. It is due to the fact that intestinal inflammation prevents the absorption of iron and vitamins, and on the other hand, it prevents the natural erythropoiesis in the bone marrow, and also accelerates the lysis of red blood cells.

Oxidative stress and anemia

Oxidative status affects various functions of normal physiological cells, but oxidative stress has toxic effects and is one of the causes for cell death and organ damage. Similarly, oxidative stress plays a role in apoptosis and cell aging, exacerbating the symptoms of many diseases, including cancer, atherosclerosis, diabetes, cardiovascular disease, thromboembolism, and neurological disorders, and also oxidative stress plays a role in hemolytic anemia. Although oxidative stress is not the main cause of these various anemia, it is mediated by several diseases,

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including hemolysis (Fibach and Rachmilewitz, 2008). In Sickle cell disease (Hebbel *et al.*, 1982, Klings and Farber, 2001, Rice-Evans *et al.*, 1986) and G6PD-deficiency, the patients are subjected to increased oxidative stress. Hemoglobin is a significant source of superoxide production in RBC and the increased ROS affects mainly the membranes of plasma (Fibach and Rachmilewitz, 2008). It causes several abnormalities of membrane and protein crosslinking, and lipid peroxidation (Rice-Evans *et al.*, 1986). Therefore, RBC longevity reduces and then hemolysis increases (Mccord, 1993) and anemia occurs (Fibach and Rachmilewitz, 2008) (**Figure 1**).

Inflammation and anemia

Anemia of inflammation (AI, formerly also called anemia of chronic disease or anemia of chronic disorders) is usually mild to moderate anemia (hemoglobin rarely less than 8 grams per deciliter) in the regulation of infection, causing inflammatory or malignant disease (Ganz and Nemeth, 2009). In inflammation and infectious diseases, inflammatory cytokines increase hepcidin. The binding of hepcidin to ferroportin destroys ferroportin, which ultimately does not transport iron to the plasma, causing anemia (Nemeth *et al.*, 2004b). The loss of ferroportin from the cell membrane reduces the proportion of iron exports to plasma. Hepcidin production by liver cells, in turn, is regulated by plasma and hepatic iron concentrations and inflammatory cytokines, mainly IL-6 (Nemeth *et al.*, 2004a, Rodriguez *et al.*, 2014). After infection, immune cells, such as neutrophils, monocytes, and dendritic cells increase dendritic cells with cell surface sensors that are mainly interleukin-1 receptor (IL-1R), scout the biological milieu for damage-associated molecular patterns. Upon stimulation of IL-1R members, a molecular cascade is initiated, culminating in the secretion of effector pro-inflammatory cytokines, such as TNF-α and IL-6 (Cavaillon, 2001, Kobbe *et al.*, 2012). The pro-inflammatory effect of IL-1R signaling is primarily mediated by a transcription element nuclear factor-kappa B (NF-kB). Inflammatory cytokines, including TNF-α, IL-1, and interferon-γ, suppress erythropoiesis in vitro (Felli *et al.*, 2005). In this regard, a study examined the effects of erythropoiesis and inflammation. It was concluded that erythropoiesis may be suppressed by increasing T-cell and monocyte activity with the simulating production of pro-inflammatory cytokines, such as TNF-α, IL-1, and interferon-γ in the bone marrow (Macdougall and Cooper, 2002) (**Figure 1**).

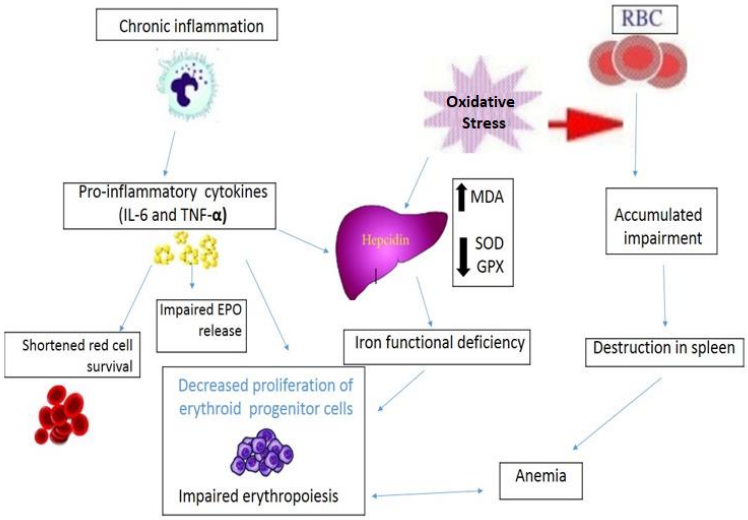

Figure 1. Inflammation and oxidative stress in anemia (Ahmadi *et al.*, 2019).

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Conclusion

Anemia is associated with oxidative stress. It is one of the causes of hemolytic anemia. Biologically active components like phenolic acids (e.g. cynarin and chlorogenic acid) and flavonoids (e.g. apigenin, luteolin, and quercetin) constituents exhibit potent ROS and free radicals scavenging ability,decreasing MDA levels (Ceccarelli *et al.*, 2010). As a result of this reduction of free radicals and MDA levels by Artichoke biologically active components, it may affect hemolytic anemia and reduce hemolysis. On the other hand, anemia reduces the body's antioxidant capacity (Aslan *et al.*, 2006, Macdougall and Cooper, 2002) and these components can increase the body's antioxidant capacity by free radicals scavenging.

Inflammatory cascade occurs following an infection that begins with NF-kB at the transcription level, followed by the secretion of inflammatory cytokines (Cavaillon, 2001, Kobbe *et al.*, 2012). Due to the effective components of artichokes, including caffeic acid, cynarin, and luteolin, it may suppress the activating pathway of NF-κB (Santos *et al.*, 2018). Therefore, inflammatory cytokines, such as TNF-α and IL-6 are not secreted and hepcidin does not increase. In this way, artichoke probably can prevent AI.

Increased inflammatory factors including TNF-α, IL-1, and interferon-γ, suppress erythropoiesis in vitro (Felli *et al.*, 2005). The high quantity of phenolic and flavonoid compounds of C. scolymus decreased inflammatory factors (García-Lafuente *et al.*, 2009) and may prevents from suppressing erythropoiesis (Macdougall and Cooper, 2002).

The evidence so far available suggests that artichoke, employed either as food item or herbal supplement, can offer additional support for the treatment of anemia. Artichokes should be used with caution in people who are allergic to it and during pregnancy and lactation(Rouhi-Boroujeni *et al.*, 2015). Designing large clinical trials on C. scolymus and evaluating its effects on anemia could be the subject of future studies.

Authors' contributions

Research project: Keramati, M., and Musazadeh, V. prepared the manuscript. The authors retain sole responsible for the content and writing of this article.

Conflict of interest

The authors declare that there is no conflict of interest.

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