

## R E V I E W

# Potential health effects of the popular compound of artichoke: Cynarin

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**Summary.** Functional food components are usually related with disease prevention. Cynarin is one of the biologically active functional food components which is the major dicaffeoylquinic acid derivative found in artichoke. Although artichoke contains very low amount of cynarin, it still duplicates the effects of artichoke. Cynarin is one of the biologically active functional food components that have potential effects on choleric and cholesterol lowering, hepatoprotective, anti-atherosclerotic, anti-HIV, antioxidative, anti-diabetic, anti-carcinogenic and immune modulator activity. To sum up, more molecular, clinical and epidemiological studies on cynarin is necessary to be able to use it as a disease preventive agent.

**Key words:** cynarin, artichoke, functional food, caffeoylquinic acid

## Introduction

Discovering biologically active functional food components and their effects are important for chronic diseases prevention. Most studies on artichoke extracts and health effects are related with antioxidant potential of phenolic compounds such as chlorogenic acid, caffeic acid, cynarin (CYN) and flavonoids (1-3). Mono- and di-caffeoylquinic acid derivatives are major polyphenols of artichoke. CYN is the major dicaffeoylquinic acid derivative of artichoke and it duplicates many effects of artichoke despite the very low amount of CYN content. In mid-century, CYN has been isolated from artichoke leaf by Italian scientists (4). Firstly, it was isolated as active principle of artichoke and called as 3,5 dimethoxy 1,4 dihydroxycyclohexane carboxylic acid (5). Afterwards, caffeoylquinic acids were classified in 1973 and the nomenclature have been changed in 1976 by IUPAC (International Union of Pure and Applied Chemistry). According to this new recommendation, when CYN

was called as 1,5-O-dicaffeoylquinic acid, it had been changed as 1,3-O-dicaffeoylquinic acid (6). CYN is the main derivative of caffeoylquinic acids which is found in both leaves and heads of artichoke (7). Methanolic extracts of artichoke contains about 1.5% CYN (3, 8). In addition, it is a key constituent of the aqueous dry extracts used in many artichoke preparations since it resists against tryptic digestion, boiling, acidification (9). Moreover, it is present only in traces in fresh or carefully dried leaf and it is formed by transesterification from 1,5-O-dicaffeoylquinic acid in hot water during the extraction process (10). Furthermore, CYN content is duplicated in cooked baby artichokes and this may be attributed to isomerization of dicaffeoylquinic acid with the heat and the esterification of caffeic acid, increasing the CYN content (11). Researches about potential health effects of CYN can be summarized as choleric and cholesterol lowering, hepatoprotective, anti-atherosclerotic, anti-HIV, antioxidative, anti-diabetic, anti-carcinogenic and immune modulator activity (12-14) (Table 1).

**Table 1.** Potential beneficial health effects of CYN

Sample	Dose	Parameter	Potential health effect	Reference
Primary hypertriglyceridemia resistant patients	750 mg 1500 mg	Total serum lipids ↓ Triglycerides ↓ Phospholipids ↓	Choleretic and cholesterol lowering	(10)
Familial type IIa and IIb resistant hyperlipoproteinaemia	250 mg 750 mg	Serum cholesterol → Serum triglyceride →		(16)
Rat hepatocytes	-	CCl <sub>4</sub> toxicity ↓	Hepatoprotective	(17)
Rat hepatocytes	3 μM	t-BPH induced MDA production ↓		(9)
Human umbilical vein endothelial cells	1 μM -100 μM	eNOS →	Anti-atherosclerotic	(19)
Human coroner artery smooth muscle cells	3 μM	iNOS ↓		(20)
MT-2 cells	25 μM -250 μM	HIV-1 replication ↓	Anti-HIV	(21)
Scavenging activity Trolox equivalent antioxidant capacity (TEAC)	14.09 μM 28.85 μM	against DPPH against ABTS	Antioxidative	(23)
3T3 cells	51 μM 45 μM	75% ↓ Fe <sup>2+</sup> induced oxidative stress 72% ↓ AAPH induced oxidative stress		(24)
BSA-glucose system	1.5 μM – 20 μM	AGE	Anti-diabetic	(25)
HeLa cells	400 μM	not cytotoxic	Cancer related effects	(21)
Leukemic cell lines and blasts of patients with acute lymphoblastic leukemia	500 μM	cytotoxic		(26)
HeLa cells FSF-1 cells hTERT-MSC cells	500 μM	cytotoxic		(27)
B-cells and T-cells	1 μM -1000 μM	CD28 related T-cell activation ↓	Immune modulator	(28)

↓: decrease; →: no effect

## Potential health effects of CYN

### *Choleretic and cholesterol lowering effects*

The study with rats demonstrated that CYN shown a significant reduction in serum cholesterol concentrations (15). The study conducted with pa-

tients with resistant primary hypertriglyceridemia shown that 750 mg and 1500 mg CYN reduced the total serum lipids, triglycerides and phospholipids concentrations (10). In contrast another study shown that the treatment with 250 mg or 750 mg CYN for three months of have no effect on serum cholesterol and tri-

glyceride concentrations of familial type IIa or type IIb hyperlipoproteinaemia patients (16). Otherwise, clinical studies showed that 60 mg - 1500 mg daily doses of CYN is effective in lowering serum cholesterol and triglyceride concentrations (14).

#### *Hepatoprotective effects*

Azdet et al (17), reported that CYN shows hepatoprotective activity against CCl<sub>4</sub> toxicity in rat hepatocytes. Another study with rat hepatocytes indicated that 3  $\mu$ M CYN reduced t-BPH induced MDA production and EC<sub>50</sub> value of CYN was 15.2  $\mu$ g/ml (9, 18).

#### *Anti-atherosclerotic effects*

Endothelial nitric oxide synthase (eNOS) is responsible for nitric oxide (NO) synthesis and it is established that CYN have not any effects on increasing eNOS promoter activity until 100  $\mu$ M (19). While eNOS has vascular protective effects induced nitric oxide synthase (iNOS) has proinflammatory effect. The study with artichoke leaf extract indicated that CYN, cyanidin, cynarosite and luteolin reduced iNOS activity and CYN was the most effective with 3  $\mu$ M (20).

#### *Anti-HIV effects*

The research results that CYN inhibits HIV-1 replication in human T-cell leukemia (MT-2) cells with 25  $\mu$ M (half maximal effective concentration-EC<sub>50</sub>) and inhibits growth of the MT-2 cells with 250  $\mu$ M (median lethal dose-LD<sub>50</sub>) (21).

#### *Antioxidative effects*

It is reported that hydroxyl groups on the aromatic ring are responsible for the antioxidant activities of phenolic compounds, the higher number of hydroxyl groups means that higher antioxidant activity. In addition, the ortho or para position of the second hydroxyl group is increased the antioxidant activity. CYN has both of this properties and it has highest antioxidant activity compare to other compounds such as chlorogenic acid, 1-caffeoylquinic acid, cynaroside, luteolin rutinoside, apigenin rutinoside, mostly found in artichoke (22). Jun et al (23), have been shown that CYN has strong antioxidant activities against DPPH (1,1-diphenyl-2-picrylhydrazyl) and ABTS (2,2'-azi-

no-bis(3-ethylbenzothiazoline-6-sulfonic acid)) radicals. Furthermore, it is demonstrated that antioxidant activity of CYN is stronger than trolox standard (half maximal inhibitory concentration-IC<sub>50</sub>: 12  $\mu$ M, 25  $\mu$ M respectively) by scavenging ABTS radicals and stronger than both trolox standard and caffeic acid (IC<sub>50</sub>: 40  $\mu$ M, 50  $\mu$ M, 70  $\mu$ M respectively) by inhibiting DPPH radicals. CYN also inhibited linoleic acid oxidation, scavenged the hydroxyl radicals and superoxide anions. It is also reported that on 3T3 cells, 51  $\mu$ M CYN inhibited oxidative stress (75%) by iron (Fe<sup>2+</sup>) and 45  $\mu$ M CYN inhibited oxidative stress (72%) induced by AAPH (2,20-azobis(2-amidinopropane)dehydrochloride) (24). Overall, the antioxidant activity of CYN depends on its' ability to scavenge ROS.

#### *Anti-diabetic effects*

Potential antiglycative effects of CYN has been shown in the bovine serum albumin-glucose system and it exhibited significant advanced glycation end products (AGE) inhibitory ability in a dose dependent manner (3  $\mu$ M - 40  $\mu$ M) (25).

#### *Anti-carcinogenic effects*

It is indicated that CYN does not have significant difference on the HeLa cells until 400  $\mu$ M (21). On the other hand, CYN has a cytotoxic effects at the rate of about 20% on leukemic cells (26). Another study showed that CYN affects normal fibroblast skin cells (FSF-1), telomerase-immortalize mesenchymal stem cells (hTERT-MSC) and cervical cancer cells (HeLa) on cell proliferation in a dose dependent manner and 500  $\mu$ M determined as cytotoxic concentration (27).

#### *Immune modulator effects*

In response to certain external stimulation T-cells initiate immune activity. Both "positive" and "negative" immune responses are important for maintaining T-cells in a healthy condition. Thus, both "over-active" and "under- active" immune responses are pathological and there are many autoimmune disease examples of "over-active" immune responses. Another research about this issue shows that CYN is a potential immune modulator agent due to blocking effects on CD28 which is T-cell receptor immune cells (28).

## Conclusion

Functional food components are usually related with disease prevention. So, the importance of functional food components and their potential health effects are increases day by day. Healthy nutrition is related with reduced disease risk and increased life quality. So, it's aimed to use the potential beneficial health effects of some most consumed foods for prevention from chronic diseases. Thus, knowing the effects of biologically active food components and their mechanisms is important to develop safety consumption suggestions and to improve personalized recommendations. CYN is one of the biologically active functional food components that have potential effects on choleric and cholesterol lowering, hepatoprotective, anti-atherosclerotic, anti-HIV, antioxidative, anti-diabetic, anti-carcinogenic and immune modulator activity. To sum up, more molecular, clinical and epidemiological studies on CYN is necessary to be able to use it as a disease preventive agent.

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