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Review Article

Artichoke (*Cynara Scolymus* Linn.): A Comprehensive Review

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ABSTRACT

Cynara scolymus Linn. (Asteraceae) is used medicinally in Europe and in USA. It is also known as "Garden artichoke" and has been subject of several chemical, pharmacological and biological studies. It is used in traditional medicine in all over the world for treatment of rheumatism, gout, jaundice and especially for dropsies. The chemical studies have underlined the presence of various classes of compounds, the main being Flavonoids, Terpenoids, Acids, Enzymes, Anthocynins and others. The extract of this plant as well as pure isolated compounds, showed multiple pharmacological activities such as Hypocholesterolaemic, Hypolipidemic, Choleric, Antioxidant, Hepatoprotective, Antistress, Hypoglycemic, Antispasmodic activity and others. In this review we have explored phytochemistry, pharmacological, biological activities, side effects and contraindications of *C. scolymus* in order to comprehend and synthesize its potential image as multipurpose medicinal agent. The plant is widely cultivated to world and its importance, as a medicinal plant, is growing substantially with increasing and stronger reports in support of its multifarious therapeutic use.

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INTRODUCTION:

Medicinal plants are of great value in the field of treatment and cure of disease. Over the years, scientific research has expanded our knowledge of the animal effects and composition of the active constituents, which determine the medicinal properties of plants. It has now been universally accepted fact that the plant drugs and remedies are far safer than that of synthetic medicines for curing the complex diseases like Cancer and AIDS.¹ *Cynara scolymus* Linn.(Family: Asteraceae) is a perennial thistle originating in Europe mainly Mediterranean region, South America and California; cultivated as vegetable.^{2, 3} It's commonly known as garden artichoke, globe artichoke,⁴ alchofra, artichaut, hathichak and hathichoke.^[4-6] Traditionally, artichoke leaves have been used as diuretic and depurative, for the treatment of rheumatism, gout, jaundice and especially for dropsies.^{7,8} It has globose, thorny capitulum of lingual florets, grows at the end of the

stem. The epicalyx is ovate to globose. The bracts are fleshy and taper into a flattened greenish of purple tip. The petals are blue, lilac or white (Figure1). The fruit is a pubescent achene 4 to 5 mm in diameter and 7 to 8 mm long. It is flecked brown and glossy. It shows a short rhizome and a strong, erect, glabrous stalk. The stalk is upto 2 m high, thickly covered in lanceolate, prickly pinnate to double pinnate leaves. The upper surface is bare and light green; the lower surface is gray and tomentosa.⁴ Although some phytochemical and pharmacological studies have been described in several monographs,^{3,4,6} but none have described the complete chemistry, pharmacology, side effects and contraindications of this important medicinal plant. Therefore, we aimed to compile an up-to-date and comprehensive review of *Cynara scolymus* L. that covers its phytochemistry, pharmacology, side effects and contraindications.

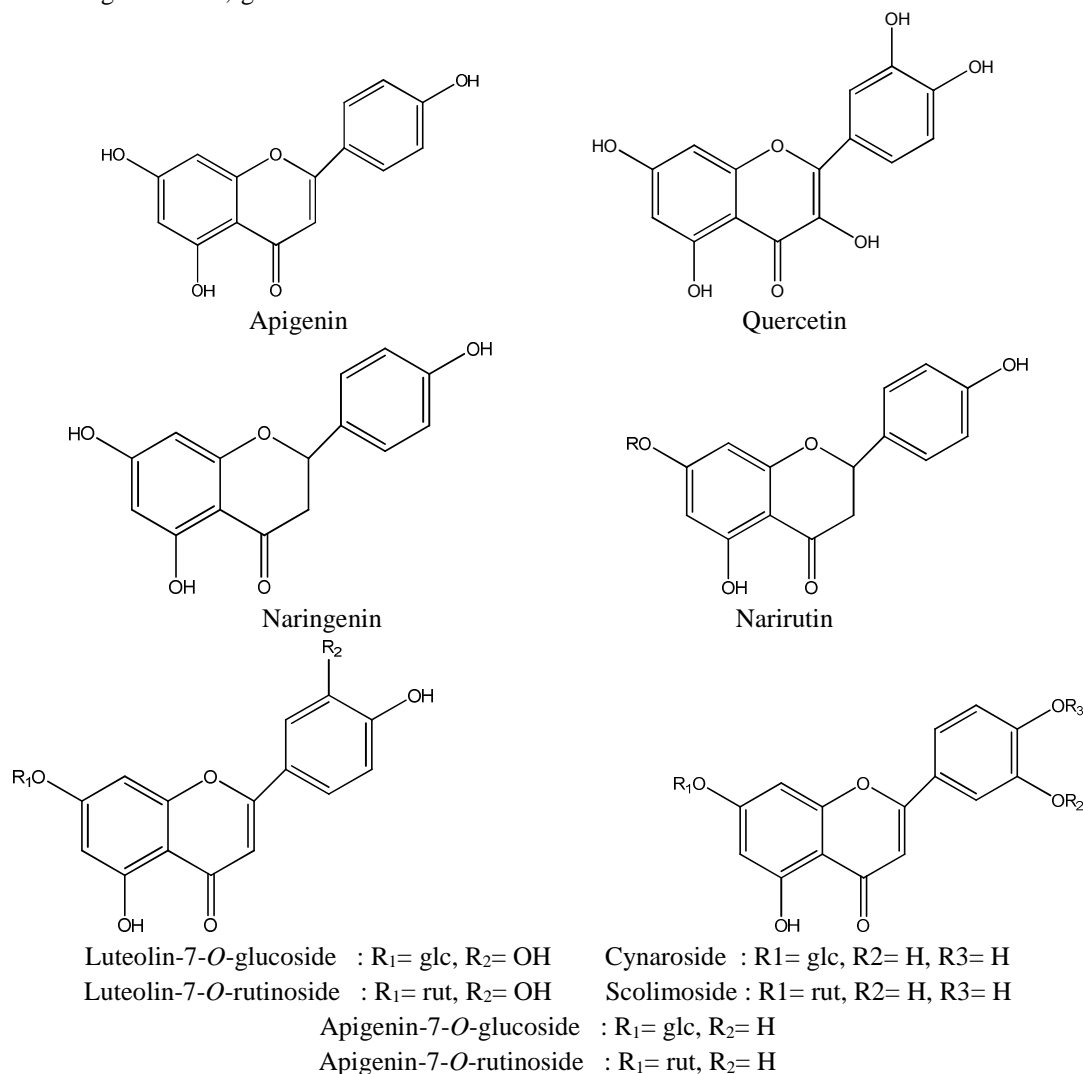
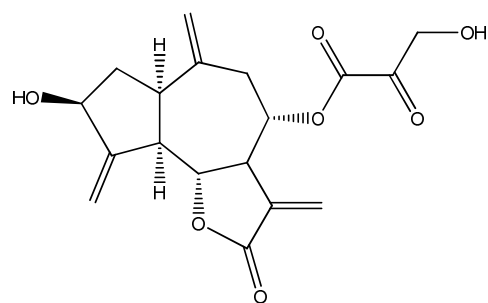
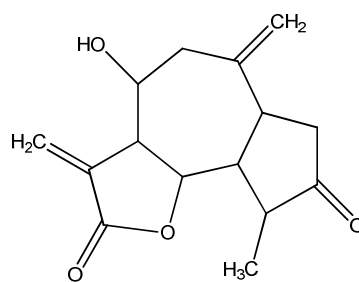


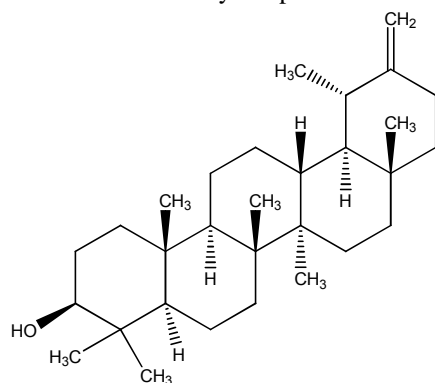
Figure 1: Structures of some Flavonoids



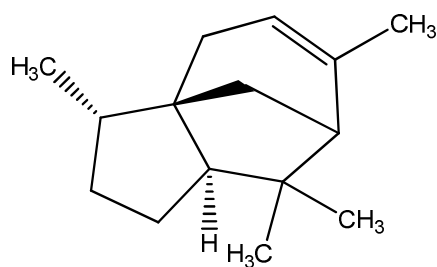
Cynaropicrin



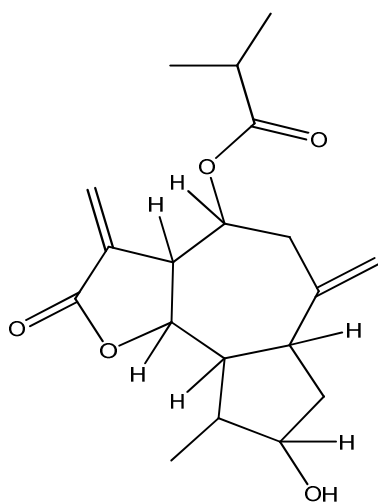
Grosheimin



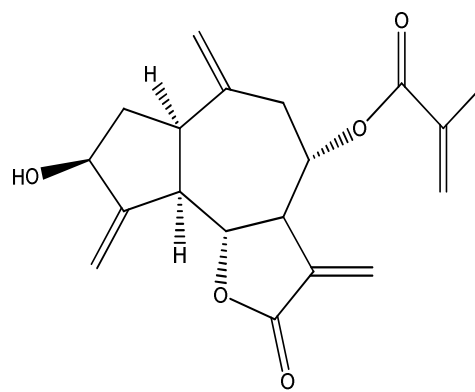
Taraxasterol



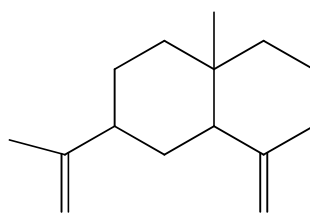
α- cedrene



Aguerin A



Aguerin B



β-selinene

Figure 2: Structure of some Terpenoids

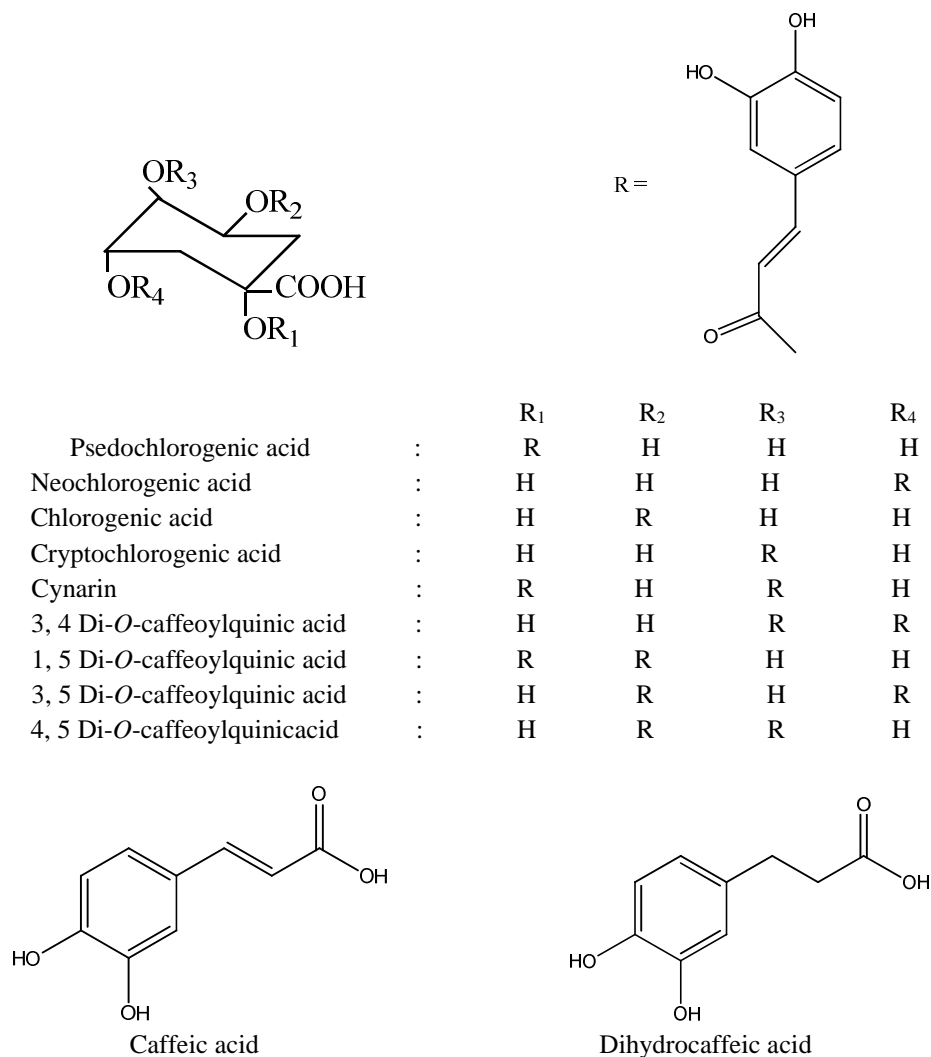


Figure 3: Structure of Caffeic acid and its derivatives

PHYTOCHEMISTRY

Flavonoids

Cynara scolymus L. is a rich source of flavonoids. Its leaves reported to contain 0.53-2.39 % of flavonoids.⁹ The various flavonoids reported in artichoke were- apigenin, apigenin-7-rutinoside, apigenin-7-*O*-rutinoside, apigenin-7-*O*-glucoside, apigenin-7-*O*-β-D-glucopyranoside,^{10,11} cynaratrioside,¹² cynaroside, scolimoside,^{13,14} narirutin, cosmoside, quercetin, rutin, scopoletin, hesperitin, hesperidoside, maritimin, esculetin-6-*O*-β-glucoside, luteolin-4'-glucoside, luteolin, luteolin-7-*O*-glucoside,^{10,15} luteolin-7-*O*-glucuronide,¹⁶ luteolin-7-rutinoside, luteolin-7-*O*-rhamnoglucoside, luteolin-7-gentiobioside,¹⁷ naringenin and isorhamnetin (Figure 1).¹⁸

Terpenoids

The various terpenoids reported in artichoke namely β-selinene (as main sesquiterpene), α-cedrene (responsible for aroma)¹⁹ cynaroscoloside A,B,C, cynaropicrin (as major bitter principle),^{13,20} aguerin A, B, dehydrocynaropicrin, cynaratriol,^{21,22} taraxasterol, Y-taraxasterol, stigmasterol, β-stigmasterol, cysarogenin,²³ grosheimin,²¹ 8-deoxy-11-hydroxy-13-chlorogrosheimin, 8-deoxy-11,13-dihydroxy grosheimin,¹⁴ phenyl acetaldehyde, decanal, eugenol, oct-1-en-3-one, hex-1-en-3-one, non-trans-2-enal (Figure 2).²⁴

Acids

The artichoke is a good source of acids like caffeic acid, dihydrocaffeic acid, 1,5-Di-*O*-caffeoylquinic acid, 1,3Di-*O*-caffeoylquinic acid (cynarin),¹⁷ 3,4Di-*O*-caffeoylquinic acid, 3,5Di-*O*-caffeoylquinic acid, 4,5Di-*O*-caffeoylquinic

acid,²⁵ cryptochlorogenic acid, chlorogenic acid, neochlorogenic acid and psedochlorogenic acid (Figure 3).^{13, 15}

Enzymes

Various enzymes have been isolated from artichoke were-cynarase A, B, C (from stigma),²⁶ polyphenol oxidase (from heads)^{27,28} and heme peroxidase (from fresh flowers).²⁹

Anthocynins

The anthocynins were reported from the heads of the artichoke. The total anthocynin content was found to be 8.4 to 1,705.4 mg/kg of dry mass. The various anthocynins found were cyanidin 3-(6"-malonyl) glucoside (major anthocynin),³⁰ cyanidin-3-caffeyl glucoside, cyanidin-3-caffeyl-sophoroside, cyanidin-3-dicaffeyl-sophoroside,²³ cyanidin3, 5-diglucoside, cyanidin3-glucoside, cyanidin3, 5-malonyldiglucoside, cyanidin3-(3"-malonyl) glucoside along with two peonidin and one delphinidin derivatives.³⁰

Amino acids

The ethanolic extract of artichoke leaves found to contain various amino acids (essential amino acids-58.29% of the total amino acid) namely- valine, threonine, methionine, isoleucine, leucine, lysine, phenylalanine, histidine, arginine and glutamic acid.³¹

Carbohydrates

The choloform extract of leaves of artichoke reported to contain Water-soluble polysaccharides (5.12%), Hot water soluble polysaccharides (1.78%), Pectinic substances (2.4%), hemicellulose (2.63%), fructose, saccharose and traces of glucose.³² Inulin (a non structural carbohydrate) has a main importance as carbohydrates.³³

Fatty acids

About 28% of fatty oil with pleasant aroma and flavour reported from the artichoke seeds. The oil contains 91.4% essential polyunsaturated and upto 9% saturated fatty acids.³⁴ The major components of the oil were lauric, myristic, palmitic, stearic, palmitoleic, oleic (44%), linoleic (40%), linolenic acids found in triacylglyceride fractions while in monoacylglyceride fraction same fatty acids with oleic (21.2%) and linoleic (6.3%) were reported.¹⁶

Others

Other components like vitamins, protein 8.93 % (leaves) and minerals also reported in artichoke.^[35]

PHARMACOLOGICAL AND BIOLOGICAL ACTIVITIES

Several researchers have reported the different pharmacological and biological activities of *C. scolymus* in various *in vitro* and *in vivo* test models. The various plant extracts as well as pure isolated compounds have been reported to exhibit hypocholesterolaemic, hypolipidemic, choleretic, antioxidant, hepatoprotective, antistress,

hypoglycemic, antispasmodic activity and others. These have been described in greater details in the following.

Hypocholesterolaemic, Hypolipidemic and Choleretic activity

Artichoke leaf extract (ALE) have been investigated for its effect on plasma lipid levels on 131 adults having plasma cholesterol level in range of 6.0-8.0 mmol/l. Out of 131 adults 75 suitable volunteers selected for trial and allowed to consume 1280 mg standardized ALE or matched placebos for 12 weeks daily, in that study cholesterol level reduce significantly by 4.2% in treated groups.³⁶ Preparations of artichoke leaf extract inhibit cholesterol biosynthesis in concentration dependent manner in studies in cultured rat hepatocytes. The artichoke extract was found to inhibit 20% inhibition at low concentration (<0.1 mg/ml) whereas inhibition was 65% at concentration 1mg/ml. In that experiment luteolin was found to be active constituent acted by inhibition of hydroxymethylglutaryl-COA (HMG-COA) reductase.^{37, 38} The aqueous extract was found to inhibit cholesterol biosynthesis in HepG₂ cells by reduction of 14C-acetate incorporation upto 60% at dose of 0.01-0.2 mg/ml.^{39, 40} In other *vitro* study, showed a concentration dependent inhibition of *de novo* cholesterol biosynthesis in cultured rat and human hepatocytes at concentration of 0.03-0.1 mg/ml of leaf extract.⁴¹ In one experiment, methanolic extract of leaves found to decrease the lipid level also. Further bioassay guided separation have shown that the activity was due to sesquiterpenes- cynaropicrin, aguerin B, grosheimin, cynaroscoloside A,B and C. The SAR studies demonstrated the importance of oxygen functional groups at 3 and 8 positions along with *exo*-methylene moiety in α -methylene- γ -butyrolactone ring.^[21] In another experiment it was found that the purified extract was more potent than total artichoke extract. In that case the reduction of plasma triglyceride and cholesterol concentration were 33% and 45% respectively when given intraperitoneally (25 mg/kg for purified extract), while it becomes 18% and 14% respectively (100 mg/kg for total extract).⁴² The powder of artichoke also found to decrease total cholesterol, serum triglyceride and LDL level *in vivo*.⁴³ In the view of choleretic and bile acid elimination effect, artichoke leaf extract found to increase bile acid flow more pronounced than that of reference compound dehydrocholic acid (DHCA) at highest dose of 400 mg/kg, while choleretic effect was similar to DHCA.^{44, 45} Various other studies have well documented for hypolipidemic, hypocholesterolaemic and choleretic activity of cynarin.⁴⁶⁻⁴⁸

Antihypertensive activity

In one study conducted using the artichoke leaf juice concentrate shows blood pressure lowering effect in mild hypertension.⁴⁹

Antioxidant activity

Jimenez-Escrig and coworker investigated the antioxidant activity of aqueous-organic extract of artichoke by three methods- a) free radical DPPH scavenging b) ferric reducing antioxidant power (FRAP) and c) inhibition of copper (II) - catalysed *in vitro* human low density lipoprotein (LDL) oxidation in male rats. It was found that 1gm (dry matter) had a DPPH activity and FRAP value *in vitro* equivalent to those of 29.2 and 62.6 mg of vitamin C and 77.9 and 159 mg of vitamin E respectively. It also showed good inhibition of LDL oxidation *in vitro*. In that experiment glutathione peroxidase enzyme was found to be elevated in erythrocytes of artichoke treated group along with decreased in level of 2-Aminoadipic semialdehyde (a protein oxidation biomarker).⁵⁰ In other study, aqueous extract of artichoke leaves was found to decrease the hydroperoxide-induced malondialdehyde (MDA) production in concentration dependent manner when studied in primary rat hepatocytes culture using tert-butylhydroperoxide assayed by LDH leakage and MTT assay.⁵¹ In one experiment, standardized extract (Hepar-SL forte) was found to show a pronounced antioxidant activity.⁵² While in different case, apigenin-7-rutinoside and narirutin were found to have a potential antioxidant activity.¹¹

Hepatoprotective activity

Artichoke leaf extract (500 mg/kg) showed hepatoprotective activity against CCl₄ induced hepatitis given orally to rats.⁵³ It also found to show hepatogenerating activity.⁵⁴ In another study it was found that the aqueous leaf extract (0.5ml daily for five days) was potent than root extract.⁵⁵ When the various component of artichoke tested for hepatoprotective activity, only cynarin and to lesser extent caffeic acid showed potent activity.⁵⁶ The preparation STIMULIV contained artichoke has been proved beneficial for management of viral and drug (antitubercular) induced hepatotoxicity.⁵⁷

Antistress activity

Zapolska-Downar and coworkers have investigated the antistress activity of aqueous and ethanolic extract of artichoke for intracellular oxidative stress stimulated by inflammatory mediators (TNF α and LPS) and ox-LDL in endothelial cells; both extracts inhibit basal and stimulated reactive oxygen species (ROS) production in a dose dependent manner by 43% and 60% for aqueous and ethanolic extract at dose of 50 μ g/ml respectively. In similar

study, in monocytes, the ROS production was reduced by ethanolic extract at dose of 50 μ g/ml upto 76%.⁵⁸ In other document, the artichoke leaf extract and its constituents have been investigated for activity against oxidative stress induced by several agents such as hydrogen peroxide and Phorbol-12-myristate-13-acetate that generate reactive oxygen species. The constituents cynarin, chlorogenic acid, caffeic acid and luteolin showed concentration- dependent inhibitory activity in these models.⁵⁹

Hypoglycemic activity

Nazni and coworkers reported that the dried powder of an artichoke had a hypoglycemic activity. For that, thirty type 2 diabetic individuals of both sexes of age 35-45 years were chosen. They were further divided into the group I (Control) and group II (Supplemented with artichoke powder through the biscuits) for 90 days. In that study it was found that, group II diabetic individuals showed the decreased in fasting blood glucose levels (163.4 ± 4.39 to 138.8 ± 3.9 mg/dl) and also post- prandial blood glucose.⁴³ As per the study of Mona Mohamed and coworkers conducted on albino rats using aqueous leaves extract of green globe (LEG) shows superior effect on glucose level control when used at concentration of 1.5 g LEG/kg/day.⁶⁰

Antispasmodic activity

The hexane, dichloromethane, ethyl acetate and butanol fractions of methanolic extract of artichoke leaves investigated for antispasmodic effect on guinea pig ileum contracted by acetyl choline. It was found that the dichloromethane fraction (0.49-1.77 mg/ml) had most potent activity than others with IC₅₀ value 0.93. Further, bioassay guided separation showed that the activity was due to sesquiterpene lactone cynaropicrin (0.049-0.086 mg/ml) with IC₅₀ value 0.065 which was 14 times more potent than dichloromethane fraction and similar to well known antispasmodic drug papaverin. However the antispasmodic effect was found probably due to reduction of calcium influx by wall of calcium channel or by inhibition of calcium release from intracellular stores.⁶¹

Antimicrobial activity

The successive chloroform, ethanol and ethyl acetate fractions of leaf, stem and head extracts of artichoke investigated for antimicrobial activity on foodborne bacterial pathogens- *B. subtilis*, *S. aureus*, *A. tumefaciens*, *M. luteus*, *E. coli*, *S. typhimurium*, *P. aeruginosa*, 4 yeasts- *C. albicans*, *C. lusitanae*, *S. cerevisiae*, *S. carlsbergensis* and 4 molds- *A. niger*, *P. oxalicum*, *M. mucedo*, and *C. cucumerinum* by using disk diffusion technique. Among them leaf extract was found to be potent against all organism tested above followed by head and stem. Further, ethanol soluble fraction showed higher activity followed by

chloroform and ethyl acetate fractions. The MICs of extracts were in the range of 1.25-10 mg/ml.⁶² In another study conducted using methanolic extract of bound phenols for (bract and heart) showed MIC values from 312-486 µg/ml against Gram negative and 486 µg/ml against Gram positive bacteria.⁶³

Bacterial enzymatic activity modifications and prebiotic effect

The artichoke extract when studied for bacterial enzymatic activity modifications on colonic bacterial enzymes (azoreductase, β -glucuronidase, β -glucosidase, nitroreductase and nitrate reductase) for 3 weeks on Wistar rats found that artichoke diet increase the weight of cecum content resulted in hypertrophy of cecum wall along with modifications of bacterial enzymes which found necessary for metabolization of glycosides and nitrocompounds.⁶¹ Whereas in different study, the aqueous extract of artichoke showed a promising prebiotic effect when assayed on *Bifidobacterium bifidum* ATCC29521. Further studies demonstrated that the effect was due to inulin.⁶⁴

Effect on irritable bowel syndrome (IBS)

Walker and coworkers reported that the artichoke leaf extract showed the significant reduction of severe symptoms of IBS in about 96% patient when tested in time span of 6 weeks. These effects were found equivalent to previous therapies generally use for IBS.⁶⁵

Endothelium protective effect

The artichoke extract was investigated to study the reactive oxygen species (ROS) generation in cultured human umbilical endothelial cells (HUVECs). It was found that the artichoke extract (25-100 µg /ml) abolished the ROS generation induced by oxy-LDL and LPS for 24 hours. So, its effect was found to be beneficial for endothelium protection.⁶⁶

Xanthine oxidase (XO) inhibition and Hypouricemic effect

Sarawek and coworkers investigated the aqueous artichoke leaf extract for xanthine oxidase (XO) inhibition and hypouricemic effect; found that ALE exhibited XO inhibition at dose of 100 µg /ml. The inhibition was found mainly due to luteolin (IC₅₀= 1.49 µmole) and weakly by caffeic acid derivatives, luteolin-7-O-glucoside and luteolin-7-O-glucuronide (IC₅₀= >100 µmole, 19.90 µmole and 20.24 µmole respectively). When that extract and above compounds were given orally to rats no observable effects were noticed on uric acid level but luteolin got slightly decreased its level when given intraperitoneally probably because of its original form.⁶⁷

Effect on vascular endothelial cells

The artichoke leaf extract was investigated for the upregulation of eNOS gene expression in human endothelial cells. It was found that the extract and its organic subfraction increased eNOS promoter activity, eNOS mRNA expression, eNOS protein expression and NO production similar to that of the Cpd 2431 (A novel compound from Aventis Pharma), furthermore it also enhances endothelium dependent vasodilation in rat aorta. Bioassay guided isolation explained that the effect was due to cynarin, chlorogenic acid, luteolin and cynaroside found mainly in organic subfractions.⁶⁸

Cytotoxic activity

Nine guinane-type sesquiterpene lactones i.e. cynarin A, B, cynarascoside C, cynaropicrin, aguerin B, grosheimin, dehydrocynaropicrin, aguerin A and cynaratriol were investigated, *in vitro*, against MCF-7 cancer cells. Among them cynaropicrin and grosheimin showed weak cytotoxicity while others didn't.⁶⁹

Milk clotting properties

This property of artichoke has been used for the preparation of cheese. In the experiment, the artichoke flower extract showed the milk clotting property useful for cheese preparation. Further studies demonstrated that the enzymes-cynarase A, B, and C might be responsible for that biological activity. Furthermore, cynarase B had found higher activity specifically by increase in peptidase activity;⁷⁰ while cynarase A had a maximum activity at pH 5.0 at 70 °C.²⁶

Effect on Mitochondrial Respiratory Chain (MRC)

In this study the artichoke extract was tested on rat liver for activity on MRC including isolated cytochrome oxidase. Extract in the range of 0.68-2.72 microg/ml demonstrated potent and concentration-dependent inhibitory activity; Concentrations > or =5.4 microg/ml entirely inhibited MRC activity. While isolated cytochrome oxidase was inhibited noncompetitively (K_i = 126 microg/ml).⁷⁰

Waste water treatment

The artichoke flower bract extract was studied for its effect on model of waste water containing a range of phenolic contaminants. It resulted that the monophenols and 4-chlorophenols were successively oxidized by extract in the presence of hydrogen peroxide (H₂O₂), while in case of L-dopa, there was no need of H₂O₂ for oxidation. These effects were probably because of the presence of isoenzymes like peroxidase and polyphenol oxidase in extract. That effect will give better eco-friendly way for the waste water treatment.⁷¹

SIDE EFFECTS AND TOXICITY

The artichoke leaf extract (Hepar-SL forte; upto 1.92 g daily for six week or six month) encountered non-specific

gastrointestinal complaints in post marketing surveillance (Phase IV study).^{47, 72} In one study, Purified artichoke extract (i.e. 265 mg/kg) was found to be more toxic than total extract (i.e. 1000 mg/kg).⁴²

CONTRAINDICATIONS

Allergic contact dermatitis, with cross sensitivity to the Compositae (Asteraceae) plants have been documented for artichoke.⁷³ In skin-prick test the women had developed type I allergy to artichoke antigens.^{74,75} However, the ingestion of artichoke also been resulted to allergy. Mainly cynaropicrin and other sesquiterpene lactone have been found to have allergic potential.⁷⁶

CONCLUSION

In this review, we have represented the information on traditional uses, phytochemistry, pharmacology, side effects and contraindications of *C. scolymus* Linn. (Asteraceae), a medicinal plant found in Europe and US. The variety of phytochemicals like Flavonoids, Terpenoids, Acids, Enzymes, Anthocynins and others have been reported from this plant. It shows variety of pharmacological activities like Hypocholesterolaemic, Hypolipidemic, Choleric, Antioxidant, Hepatoprotective, Antistress, Hypoglycemic, Antispasmodic activity and others. Taking great concern of this medicinal plant, it can be advocate as safe, highly important medicinal plant for mankind.

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