O MUNDO DA SAÚDE

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Analysis of secondary metabolites present in the plants *Cynara scolymus L* and *Artemisia absinthium L* during the treatment of dyslipidemia

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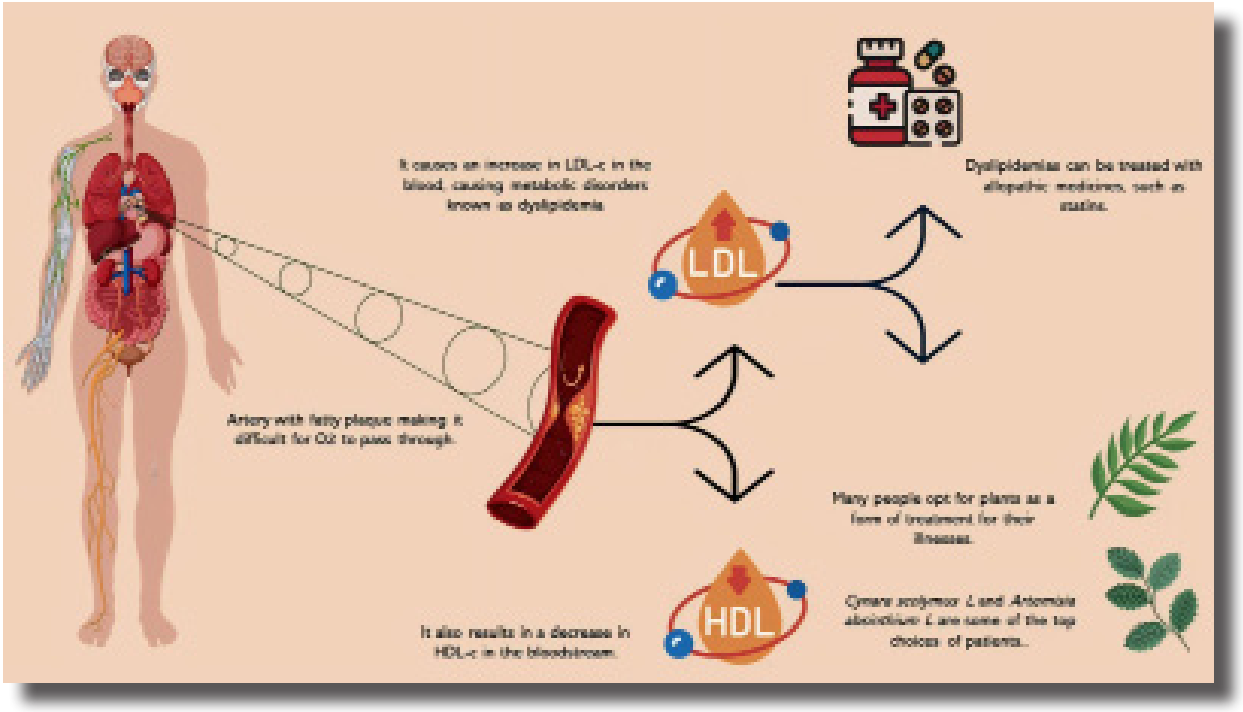
Graphical Abstract



Abstract

The use of medicinal plants as a form of treatment for various diseases is a tradition that has spanned generations for thousands of years. Ancient people used to use specific parts of some vegetables to make teas and dressings for wounds. Even today, many people prefer natural forms as a treatment for their comorbidities, especially as adjuvants in the fight against dyslipidemia. The present work aimed to analyze the plants *Cynara scolymus L* and *Artemisia absinthium L* to confirm the presence or absence of specific proteases against hypercholesterolemia. The research was carried out by screening the plants using the RCSB software (https://www.rcsb.org/). In the end, it can be confirmed that the *Cynara scolymus L* plant meets the prospects for treating hypercholesterolemia, while *Artemisia absinthium L* did not present sufficient values that are effective in the treatment.

Keywords: *Artemisia Absinthium L. Cynara Scolymus L.* Hypercholesterolemia.

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INTRODUCTION

Dyslipidemias (DLPs) are characterized as metabolic diseases, in which there is an increase in plasma levels of cholesterol and/or triglycerides (TG), low-density lipoprotein (LDL-c) and a reduction in high-density lipoprotein (HDL-c). It is considered hypercholesterolemia when there is an isolated increase in LDL-c, and hypertriglyceridemia, which is an isolated increase in TG[1,2]. DLPs can be classified as primary, when triggered by genetics, or secondary, when caused by other diseases such as diabetes *mellitus*, obesity, alcoholism and hypothyroidism. They may also be associated with the individual's lifestyle, such as a sedentary lifestyle and the indiscriminate use of some medications such as corticosteroids and anabolic steroids[3].

Currently, sedentary behavior associated with inadequate eating habits has been a potential factor in the development of cardiometabolic diseases, especially in children and adolescents[4]. Thus, the great change in the lipid profile contributes to the development of other disorders, such as atherosclerosis, coronary artery disease and systemic arterial hypertension. According to the latest report published by the Ministry of Health, there were around 100,000 deaths in Brazil due to high cholesterol and heart attacks resulting from this disorder, thus posing cardiovascular diseases (CVD) as a major challenge to global health[5,6].

According to the World Health Organization (WHO), by 2030 CVDs will continue to be the main cause of death, affecting at least 23 million people worldwide. Due to this, lipid content has been the target of investigations as a crucial factor in the prevention of atherosclerotic, cardiovascular and liver diseases[3,7].

An alternative that has become very effective for controlling hypercholesterolemia is the use of herbal medicines and medicinal plants, as adjuvants to pharmacological treatment. Medicinal plants such as *Cynara scolymus L* (artichoke) and *Artemisia absinthium L* (wormwood) have choleretic and cholagogue properties, in addition to having secondary metabolites that help reduce cholesterol levels in the bloodstream, reinforcing their role in the treatment of dyslipidemia[8,9,10,11].

Thus, the present work aimed to study the presence of secondary structures in the plants *Cynara scolymus L* and *Artemisia absinthium L*, in order to verify whether the most prevalent compounds in these plants have action against hypercholesterolemia, in addition to determining the inhibitory potential of *Cynara scolymus L* and *Artemisia absinthium L* in high cholesterol proteins and define the most prevalent proteases in this disease.

METHODOLOGY

A descriptive study with a quantitative approach was carried out to determine the number of compounds present in plants and relate them to the proteases present in hypercholesterolemia. The samples were chosen for analysis based on articles that associated the plants *Cynara scolymus L* and *Artemisia absinthium L* with a decrease in serum cholesterol levels.

The research was carried out in April 2023, in the computer laboratory of *Faculdade Independente do Nordeste*, using software accessed through the website https://www.rcsb.org/, using information from the plants *Cynara scolymus L* and *Artemisia absinthium L*, collected in books and articles. The main compounds present in the samples were then identified.

Through a bibliographical survey using more recent articles and studies from the Scielo, LILACS and PubMed platforms, data were obtained to determine the most prevalent compounds present in *Cynara scolymus*

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L and *Artemisia absinthium L*, in addition to realizing the structures of these metabolites, their description, the from the website https://www.rcsb.org/ and determination of the Tanimoto Coefficient, based on the chains found in each compound, correlating with the values found for the hypercholesterolemia disease. At the end, it was discussed about the possible use or not of the plants found for the treatment of dyslipidemia.

At the end of data collection, they were transcribed and tabulated using a Microsoft Office Excel 2016 spreadsheet containing the variables under study, presented in the form of frequency and percentage. For the analysis and interpretation of research data, the qualitative analysis method was used, describing in a comparative table format the main metabolites found.

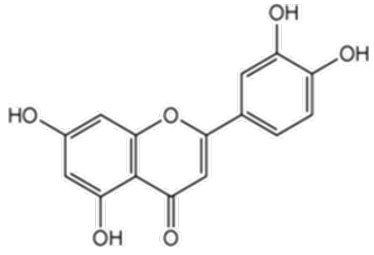
The results were based on inclusion criteria, encompassing all the major secondary metabolites in the two plants for analysis, excluding all compounds in smaller quantities that were not related to the treatment.

RESULTS

Research was carried out on the most abundant metabolites in the plants *Cynara scolymus L* and *Artemisia absinthium L*, and after that, these compounds were screened to discover the chain value of each one to be calculated considering the Tanimoto Coefficient (TC), a metric system that will measure the similarity between two sets in an element, evaluating the ratio between the intersection of these sets[12]. The compounds were grouped in tables 1 and 2 presenting their name according to IUPAC (International Union of Pure and Applied Chemistry), their molecular weight, structural formula, the acronym corresponding to the compound on the platform and its value represented by letters.

On the website https://pt.planetcalc.com, data on the compounds were added together with the data found on hypercholesterolemia and when compared, results of their similarity were obtained. As established by TC, values equal to 1 show good similarity between the sets, and values less than 1 show low interaction between them[12].

Table 1 - Most prevalent compounds in *Cynara scolymus L* samples, Vitória da Conquista, Bahia, 2023.

Cynara scolymus L	
	**CHLOROGENIC ACID** **IUPAC NAME**: 5-caffeoylquinic acid **MOLECULAR WEIGHT**: 354.31 g/mol **FORMULA**: $C_{16}H_{18}O_9$ **ACRONYM:** 6LK2 **CHAIN*:*** G, M, R, U

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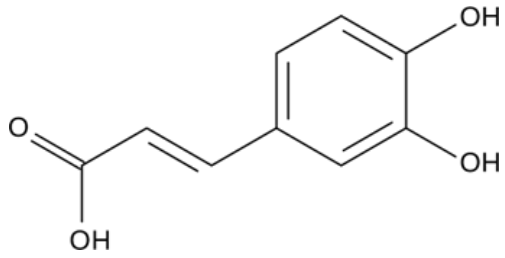
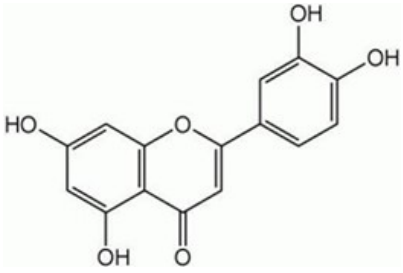
Cynara scolymus L



CAFFEIC ACID

IUPAC NAME: Caffeoylquinic Acid
MOLECULAR WEIGHT: 180.16 g/mol
FORMULA: $C_9H_8O_4$
ACRONYM: 1KYZ
CHAIN*:* A, B, C

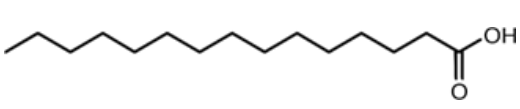


LUTEOLIN

IUPAC NAME: 22-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one
MOLECULAR WEIGHT: 286.24 g/mol
FORMULA: $C_{15}H_{10}O_6$
ACRONYM: 4QYA
CHAIN*:* C, E

Table 2 - Most prevalent compounds in *Artemisia absinthium L.* samples, Vitória da Conquista, Bahia, 2023.

Artemisia absinthium L



PENTADECANOIC ACID

IUPAC NAME: n-Pentadecanoic acid
MOLECULAR WEIGHT: 242.403 g/mol−1
FORMULA: $C_{15}H_{30}O_2$
ACRONYM: 7WPW
CHAIN*:* B

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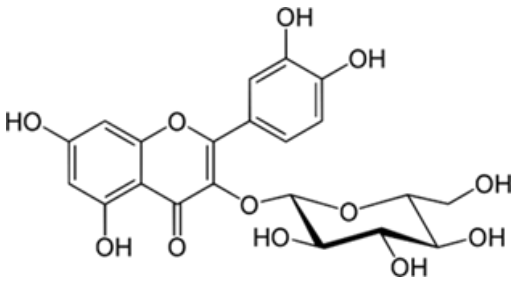
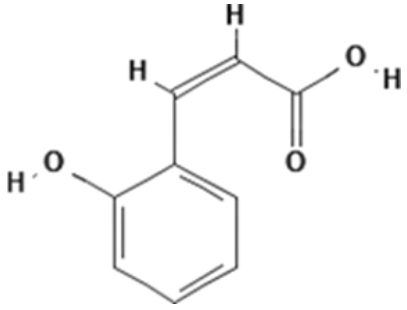
... continuation Table 2

Artemisia absinthium L



ISOQUERCETIN

IUPAC NAME: 3-(β-D-Glucopyranosyloxy)-3′,4′,5,7 tetrahydroxyflavone
MOLECULAR WEIGHT: 464.379 g/mol
FORMULA: $C_{21}H_{20}O_{12}$
ACRONYM: 6QCE
CHAIN*:* J, U



COUMARINIC ACID

NOME IUPAC: 4' Hydroxycinnamic Acid
IUPAC NAMECULAR: 164.160 g/mol
FÓRMULA: $C_9H_8O_3$
ACRONYM: 4EYO
CHAIN*:* B

Research was carried out on the action on therapeutic targets of the six metabolites found in the two plant samples mentioned in the research. In Tables 2 and 3, the main targets of each compound were grouped together with the result obtained from the Tanimoto Coefficient for comparison.

Table 3 - Activities found in the metabolites evaluated. Vitória da Conquista, Bahia, 2023.

Cynara scolymus L	Target	TC
Chlorogenic Acid	LDL-c	1
Caffeic Acid	TG	0.75
Luteolin	HMG-Coa	0.85

Table 4 - activities found in the metabolites evaluated. Vitória da Conquista, Bahia, 2023

Artemisia absinthium L	Target	TC
Pentadecanoic Acid	-	0
Isoquercetin	LDL-c	0.5
Coumarinic Acid	-	0.25

From the tables it can be seen that chlorogenic acid was the only one to present a coefficient equal to 1, having similarity only in therapeutic target with isoquercetin. Caffeic acid and luteolin were the components with values closest to the ideal, with 0.75 and 0.85, respectively, showing their action directly on triglycerides and cholesterol synthesis. Isoquercetin, despite acting on the same target as chlorogenic acid, showed a lower result than recommended, presenting value of 0.5, and coumarin acid, which presented a coefficient of 0.25, did not show any effect on any target related to hypercholesterolemia.

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DISCUSSION

LDL-c is a lipoprotein made up mostly of cholesterol, and a high expression of its receptors causes an increase in cholesterol in the blood, becoming a major therapeutic target in the discovery and treatment of hypercholesterolemia and an important predictor of risk for cardiovascular diseases[13].

Another finding of great importance was the role of caffeic acid on triglycerides, which are fats formed from three fatty acid molecules linked to a cholesterol molecule, constituting one of the most important forms of energy storage in the body. Changes in these components combined with a decrease in HDL-c may favor the development of other metabolic disorders[13,14].

The phenolic compounds present in Cynara scolymus L showed inhibition of low-density lipoprotein (LDL-c) activity, associated with increased mobilization of free fatty acids from peripheral fat deposits that led to the active conversion of fatty acids to phospholipids and cholesterol[15]. In other studies, it was reported that artichoke can be used in the treatment of hypercholesterolemia, with a marked decrease in serum cholesterol seen through the inhibitory effects on cholesterol synthesis carried out by the secondary metabolites present[16]. It can also be observed that herbal medicine formulations from this plant can help in the treatment of various pathologies, and can be used in combinations or even replacing some allopathic medicine.

Research has proven the plant's effectiveness in reducing the oxidation of LDL-c in the blood, thus reducing the risk of atherosclerosis. They also demonstrated good tolerability of the dry extract of the artichoke plant in the treatment of hypercholesterolemia, reducing plasma lipid levels. It has also been reported that herbal treatment with artichoke can be a possible option to allopathic drugs (statins), demonstrating several benefits due to its antioxidant and hypocholesterolemic properties, without reports of adverse effects[15,16].

In relation to *Artemisia absinthium L*, research has shown that the herb santa plant has low or no performance in combating dyslipidemia, as there are few phenolic compounds acting on the therapeutic targets necessary to reduce cholesterol, LDL-c and TG levels[17,18,19].

Chlorogenic acid is a phenolic compound in which the literature reports several studies on its beneficial effects on health, based on its antioxidant properties, slowing the oxidation process produced by free radicals, protecting cells and combating the development of atherosclerotic diseases, dyslipidemia , cardiovascular diseases, hypercholesterolemia, among others[11,20].

Caffeic acid, belonging to the group of hydroxynamic acids, has a natural origin and can be found mainly in plants and fruits. Several pharmacological activities are described, mainly anti-atherosclerotic effects, through the reduction of LDL-c oxidation and the reduction of nuclear factor, in addition to hepatoprotective properties and the reduction of the percentage of body fat and the effects of obesity on bone tissue. It has also been demonstrated that caffeic acid is one of the main responsible for modifications in liposaccharides (LPS), mainly involved in inflammatory responses[21,22]. Luteolin was the flavonoid compound found in greatest abundance in the plant *Cyanara scolymus L*, playing a very

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important role as an antioxidant, acting especially in the inhibition of LDL oxidative stress and an inhibitory effect on cholesterol synthesis, in addition to being a promoter of carbohydrate metabolism and a great modulator of the immune system[16,23].

The last compound found was isoquercetin which, despite showing lower levels in the samples, its presence also proved to be of great importance in acting against hypercholesterolemia. Being a glycoside derived from quercetin, it has proven to be quite effective in improving the accumulation of hepatic lipids, reducing the effects of cholesterol through the inhibition of pancreatic lipase and cholesteric esterase activities, as well as inhibiting the solubility of cholesterol micelles[24].

The presence of these metabolites in the samples and their values found when compared to the factors identifying hypercholesterolemia prove that the plants used have significant efficacy in reducing cholesterol and can be used as adjuvants in the treatment of dyslipidemia. This finding could influence the area of pharmaceutical research for the production of new medicines that act to combat dyslipidemia.

CONCLUSION

Based on research carried out in the literature and tests carried out on the software, it can be concluded that the plant *Cynara scolymus L*, popularly known as artichoke, can help in the treatment of dyslipidemia, especially hypercholesterolemia, as an adjuvant medicine, since it cannot act alone. Changes in lifestyle, balanced diets and medication are necessary to reduce and control cholesterol levels. The plant *Artemisia absinthium L*, despite also containing flavonoid compounds (which have already been proven to be effective in reducing LDL-c), presented lower amounts of phenolic compounds, being insufficient in the treatment of dyslipidemia.

For the pharmaceutical industry, the results of this research can contribute as a form of pharmacological innovations for the production of new herbal medicines replacing or being associated with current substances, making it possible to reduce side effects and increase lipid-lowering effects.

CRediT author statement

Conceptualization: Menezes, DC; Santos, TA; Portela, FS. Methodology: Menezes, DC; Santos, TA. Validation: Menezes, DC; Santos, TA; Portela, FS. Statistical analysis: Menezes, DC; Santos, TA; Portela, FS. Formal analysis: Menezes, DC; Santos, TA; Portela, FS. Investigation Menezes, DC; Santos, TA; Portela, FS. Resources: Menezes, DC; Santos, TA; Portela, FS. Writing-original draft preparation: Menezes, DC. Writing-review and editing: Santos, TA; Portela, FS. Visualization: Menezes, DC; Santos, TA; Portela, FS. Supervision: Santos, TA; Portela, FS. Project administration: Menezes, DC; Santos, TA; Portela, FS.

All authors have read and agreed with the published version of the manuscript.

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