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Rosmarinic acid as a potential anti-hyperlipidemic agent

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Abstract

Rosmarinic acid (RA) is a natural phytochemical that occurs in numerous plants including *Rosmarinus officinalis.* This bioactive compound is widely reported to exert various pharmacological effects including anti-hyperlipidemic activity. In this study, we reviewed the literature data on RA and hyperlipidemia research. *In silico, in vitro,* and *in vivo* studies were retrieved from in Scholar, PubMed, ScienceDirect, Web of Science, and Scopus. The *In silico* studies revealed that RA possesses squalene synthase and 3-hydroxy-3-methylglutaryl–coenzyme A reductase enzymes inhibiting activity. Additionally, *in vitro* reports revealed that RA exerts remarkable lipid-lowering effects and also exhibits anti-adipogenic and anti-atherosclerotic activities. The lipid-lowering action was modulated by numerous mechanisms including the regulation of anti-inflammatory and antioxidant signaling pathways. Moreover, *in vivo* studies revealed that RA alleviates hyperlipidemia in animal models by modulating the expression of genes involved in hyperlipidemia as well as the regulation of gut microbiota and anti-inflammatory pathways. We conclude that RA is a multi-target anti-hyperlipidemic agent. Moreover, we suggest that the use of this bioactive compound as an anti-hyperlipidemic drug would be an effective pharmacological strategy that could provide promising options for the treatment and prevention of hyperlipidemia and its related disorders including atherosclerosis.

Keywords

Rosmarinic acid; hyperlipidemia; lipid-lowering actions

Introduction

Hyperlipidemia is a clinical condition that encompasses diverse genetic and acquired disorders characterized by an elevation of lipid levels within the body (1). This medical condition is considered one of the main causes leading to cardiovascular and cerebrovascular disorders, mainly atherosclerosis (2). Chemically synthesized drugs, including fibrates (3) and statins (4), are the most commonly prescribed to treat hyperlipidemia and its related diseases (5). However, the use of these agents may cause several side effects, such as liver toxicity (6), diabetes mellitus, central nervous system complaints, and muscle symptoms (7). Therefore, it is essential to search for natural lipid-lowering agents due to their safety compared to chemical drugs.

Recently, plant-based compounds have become essential players in looking for safer and newer alternative drugs (8,9). Indeed, these phytochemicals can alleviate hyperlipidemia through several ways,

including the regulation of lipoprotein metabolism (10), gut microbiota (11), inflammatory pathways (12), and lipid absorption (13). Rosmarinic acid (RA) is one of these bioactive natural chemicals due to its remarkable pharmacological properties and therapeutic effect against cardiovascular disease (14). Therefore, we carried out this mini-review to highlight the lipid-lowering potential of this phenolic compound.

Methodology

This work was carried out by retrieving eligible papers that reported the anti-hyperlipidemic effect of RA (in silico, *in vitro*, and *in vivo* studies) in the following reliable sources: Google Scholar, PubMed, ScienceDirect, Web of Science, and Scopus. The used keywords were rosmarinic acid, hyperlipidemia, regulating activity, lipid-lowering effect. Then, the relevant articles were used to extract various information (type of experiment and technique, doses, and results). Moreover, we highlighted the action mechanisms of RA on hyperlipidemia and related diseases and we discussed the obtained results.

Results

Rosmarinic acid-chemical nature and biosynthesis

Rosamarinic acid was first obtained from *Rosmarinus officinalis* L. (Lamiaceae) and occurs in numerous Lamiaceae plants and also can be found in other plant families such as Apiaceae and Boraginaceae (15). RA is an ester of two compounds which are 3,4-dihydroxyphenyl lactic acid and caffeic acid (16). These phenolic compounds contain in their structure one or more aromatic ring that has at least one hydroxyl group (17). They are powerful antioxidants and exert numerous pharmacological actions. RA has 2 phenolic rings: one is derived from tyrosine pathway through dihydroxyphenyl-lactic acid whereas the other one from phenylalanine pathway through caffeic acid (Fig.1)(18).

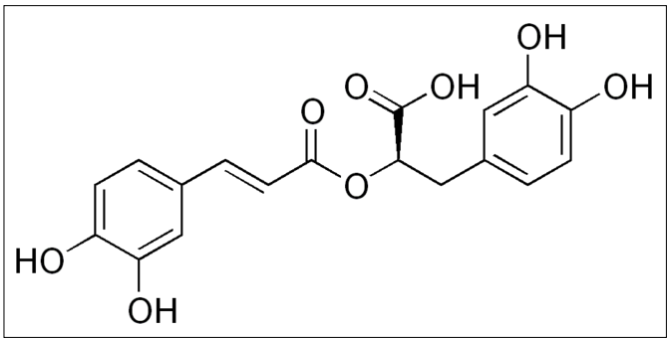

Fig. 1. Chemical structure of rosmarinic acid

Pharmacological activities

The literature reports evidenced the important bioactivity of RA. This phenolic compound was reported to exhibit a broad range of pharmacological and biological properties (Table 1).

Rosmarinic acid and hyperlipidemia

In silico studies

The correlation between the structure of rosmarinic acid and its effect on hyperlipidemia has not been extensively studied. There have been limited studies investigating this relationship (24,25). The process of producing cholesterol involves multiple steps of enzymatic biosynthesis. Squalene synthase (SQS) (26) and 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMGR) catalyze committed steps in cholesterol biosynthesis (27). Thus, the down-

Table 1. Pharmacological significance of RA.

RA or extract rich in RA (ER-RA)	Pharmacological activity	Animal system/*in vitro*	Dose applied	Important outcome of the study	Reference
RA	Cardioprotective	C57BL/6J male mice subjected to I/R injury	100 mg/kg	↓ IS (14.5%), EF (-23.4%), FS (-18.4%), myocardial injury enzymes CK-MB, cTnI, DHE-ROS, ACO activity (-2.1 mU/mg protein), OGDH protein and mRNA levels.	(19)
		Cardiac muscle cells (I/R injury)	50 µM	↓ LDH; DHE-ROS; ACO activity; OGDH protein and mRNA, p-IκB-a, and p-NF-κB	
ER-RA	Hepatoprotective	*Wistar* rats injected with CCl4	200 mg/kg	↓ AST, ALT, ALP, and LDH; malondialdehyde. ↑ total protein and albumin	(20)
RA	Anticancer	Human MARK4 protein (*In vitro*)	0–18 µM	↓ MARK4 activity (IC_{50}=6.204 µM)	(21)
		MD simulation(*In silico*)	-	↑ affinity to MARK4 (K = 10^7 M^{-1})	
RA	Anti-inflammatory	Male C57BL/6 mice (DSS-Induced Colitis)	5, 10, 20 mg/kg/day	↑ mucus production, Nrf2, and HO-1 ↓ myeloperoxidase activity, TNF-α production, NLRP3, caspase-1, IL-1β	(22)
RA	Anti-diabetic	Rats (STZ-induced diabetes)	30 mg/kg/ day	↑ gene expression of Akt1 and Akt3	(23)
		Glycation of human DNA (*in vitro*)	25 µM	↓ Glycation induced DNA damage	

↑: elevation, ↓: reduction, **I/R**: ischemia reperfusion, **IS**: infarct size, **FS**: left ventricular fractional shortening, **EF**: left ventricular ejection fraction, **CK-MB**: creatine kinase-MB, **cTnI**: cardiac troponin I, **DHE**: Dihydroethidium, **ACO**: aconitase, **OGDH**: Oxoglutarate dehydrogenase; **AST**: aspartate transaminase, **ALT**: alanine transaminase, **ALP**: alkaline phosphatase, **LDH**: lactate dehydrogenase; **MARK4**: Microtubule affinity regulating kinase 4, **DSS**: Dextran sulfate sodium, **NLRP3**: NLR family pyrin domain-containing 3, **IL-1β**: Interleukin-1 beta, **STZ**: streptozotocin.

regulation of the synthesis and the activity of these enzymes would be important target for lowering lipids. In this overview, the effect of RA and other 11 phytoconstituents of *Mentha piperita* was tested on the docking behavior with HMGR and SQS (24). The findings of this study revealed that RA had interaction energies of 42.4 and 46.8 kcal/mol with HMGR and SQS ligands respectively, suggesting potential inhibiting effects. Similar conclusions were reported in another study, in which it was found that RA was capable to bind with HMGR with a binding energy value of 10.90 kcal/mol (25).

In vitro studies

Several studies reported the anti-hyperlipidemic actions of RA using several *in vitro* models. RA was tested on oleic acid-induced steatosis in hepatic (HepG2) cells (28). The findings of this study indicated that RA exerted significant hypolipidemic potential by reducing the elevated levels of triglycerides (TGs) and total cholesterol (TC). Moreover, RA reduced steatosis *via* the suppression of oxidative damage markers and regulation of endoplasmic reticulum stress-induced autophagy. Furthermore, the effect of RA on adipogenesis was tested on human adipocytes. This study revealed that RA exhibits significant anti-adipogenic and anti-inflammatory properties. The anti-adipogenic effect was mediated by abrogating the downstream translation of peroxisome proliferator-activated receptor gamma (PPARγ), adiponectin, and CCAAT/enhancer binding protein alpha (C/EBPα), along with the regulation of pro-inflammatory factors namely interleukin 17A (IL-17A) and transforming growth factor beta 1 (TGFβ1) (29). In addition, another study was conducted to understand the mechanisms of RA on cholesterol efflux using oxidized low-density lipoprotein induced alterations in macrophages model (30). The findings revealed that RA elevated the expression of ATP-binding cassette transporter G1 (ABCG1) and A1 (ABCA1) thereby improving cholesterol efflux in macrophages. The elevation of ABCA1 and ABCG1 is a strategic target for stimulating reverse cholesterol transport, thus lowering the risk of atheromatous plaque formation (31).

In vivo studies

Several experiments have consistently supported the contention that RA alleviates hyperlipidemia in animal models. The effect of RA on lipid parameters was conducted in ovariectomized female rats (32). Rats were treated orally with RA (at 50 mg/kg) through oral route daily for 1 month. The results showed that RA significantly decreased both plasmatic cholesterol and triglyceride levels when compared with the ovariectomized controls. Another study assessed the effect of RA-rich extract from *Ocimum basilicum* on lipid profiles of hyperlipidemic mice fed with high-fat diet (HFD) (33). Mice were treated for 9 weeks with daily gavage at a dose of 0.2 g/kg. The findings of this study revealed that RA-rich extract decreased in significant manner the levels of TC, LDL-C, and TGs. Similar findings were noted in hepatic TC and TGs levels. Furthermore, the RA-rich extract prevented mice plasma lipoprotein oxidation in a dose-dependent manner, with an IC_{50} value of 10.26 ± 0.87 µg/mL. Another scientific investigation assessed the effect of RA on lipid metabolism in HFD-induced hyperlipidemic C57BL/6J mice (34). Mice were supplemented daily with RA at two doses (50 or 100 mg/kg) via gastric gavage for 2 months. The findings showed that treatment with RA significantly decreased body weight, and TC and TGs levels in either blood or liver. In mice hepatic tissues, RA elevated the gene expression of cholesterol uptake-associated receptors including LDL receptor and scavenger receptor B type 1. Moreover, RA particularly elevated the expression level of ATP-binding cassette G8 (ABCG8) and G5 (ABCG5) transporters, cholesterol excretion molecules, and cholesterol 7 alpha-hydroxylase A1 (CYP7A1). In addition, RA facilitated the oxidation of fatty acid through the activation of AMP-activated protein kinase (AMPK), promoting carnitine palmitoyl transferase 1A (CPT1A) induction. Recently, it has been found that *Trichodesma khasianum* RA-rich extract exerted a protective action against dyslipidemia and gut microbiota dysbiosis in hyperlipidemic C57BL/6J mice (35). In this study, mice were intragastric supplemented with the extract at two doses (125 or 250 mg/kg) for 4 months. The findings revealed that *Trichodesma khasianum* RA-rich extract significantly lowered body weight and fat ratio, adipose tissue accumulation, tumor necrosis factor-α (TNF-α), blood lipids, and malondialdehyde. This effect was correlated with the reduction of *Firmicutes*/*Bacteroidetes* ratio and amelioration of the relative abundance of gut microbiota such as *Lactobacillus*, *Bacteroidetes,* and *Muribaculaceae*.

Discussion

Overall, statins are the most frequently prescribed medications for the management and prevention of cardiovascular diseases and lipid disorders (36). They are the primary drugs that decrease cholesterol production (37). According to the findings of *in silico* and *in vitro* studies, it has been found that statins work by obstructing HMGR, the rate-limiting enzyme in cholesterol biosynthesis, through competitive inhibition (38,39). Similar conclusions were reported for RA. Indeed, *in silico* characterization revealed that RA possesses HMGR and SQS inhibiting potential. Inhibiting these enzymes is important in cholesterol regulation. However, this is not the only mechanism of RA in lowering lipids. *In vitro* studies provided additional insights into the hypolipidemic potential of this molecule. First, it was found that it was capable of reducing steatosis in hepatic cells by alleviating oxidative damage markers and regulating endoplasmic reticulum stress-induced autophagy (28), providing a promising application for RA as a potent adjunct for treating fatty liver disease in the absence of approved drugs. Secondly, RA revealed its potential to exhibit significant anti-adipogenic and anti-inflammatory properties in human adipocytes (29). Adipogenesis remains the top cause of the pathogenesis of obesity and associated complications (40). Moreover, impaired adipogenesis and resultant adipocyte dysfunction increases the release of free fatty acids, and promote several disorders including systemic inflammation and lipotoxicity (41). PPARγ and CCAAT/EBPα are considered to

be modulating adipogenesis at the early stage, whereas adiponectin is responsible for the regulation of adipocyte maturation (42). These two stages are both regulated by RA, suggesting anti-obesity potential. Thirdly, RA was capable of enhancing cholesterol efflux (30). Cholesterol efflux pathways have beneficial effects against inflammation and the development of atherosclerosis by inhibiting the growth of hematopoietic stem and progenitor cells, as well as inflammation and activation of inflammasomes in macrophages. Additionally, these pathways prevent the accumulation of cholesteryl esters in macrophages, which is responsible for the formation of macrophage foam cells (43). Other *in vitro* studies supports the preventive effect of RA against atherosclerosis through the modulation of antioxidant and anti-inflammatory pathways (44,45). This makes RA an interesting agent for cholesterol lowering therapy and preventing atherosclerosis. Furthermore, *in vivo* studies confirmed the potent anti-hyperlipidemic activity of RA in animal model. The intake of RA and RA-rich extracts has proven lipid-lowering effects through several mechanisms including the regulation of antioxidative markers, inflammatory pathways, gut microbiota, and lipid metabolism.

Prospects and Conclusion

The reviewed findings of previous reports prove that RA exerts anti-hyperlipidemic effects through the regulation of several cellular and molecular targets. *In silico* characterization revealed that RA possesses remarkable HMGR inhibitory potential, *in vitro* studies showed that this molecule exerts significant anti-hyperlipidemic activity and also exhibits anti-adipogenic and anti-atherosclerotic effects, and *in vivo* studies revealed that RA can alleviate hyperlipidemia through the modulation of lipid metabolism, gut microbiota, antioxidative markers, and inflammatory pathways. Thus, the use of RA as an anti-hyperlipidemic drug would be an effective pharmacological strategy that could provide promising options for the treatment of cardiovascular disease including atherosclerosis. It is recommended to carry out clinical trials to confirm the reported effects of RA on humans.

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Authors contributions

OB, HE, and AA conceived and wrote the manuscript. CA, ME and SA reviewed and edited the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: **:** The authors declare that they have no conflicts of interest.

Ethical issues: None

Supplementary data

Graphical abstract of rosmarinic acid regulation mechanisms

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