Review Article

A review of the pharmacological effects of Anacardiaceae family on controlling lipid profile (dyslipidemia)

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ABSTRACT

Dyslipidemia is a chronic non-communicable disease (CNCD), induced by abnormalities in lipid metabolism resulting from excess intake of cholesterol, trans and saturated fats. Dyslipidemia is indicated by increased plasma total cholesterol, low-density lipoprotein (LDL) and triglyceride levels, and lower high-density lipoprotein (HDL) levels. Common treatments for dyslipidemia do not indicate ideal plasma cholesterol levels for every patient, which means better treatment is required. Some species of the Anacardiaceae family have pharmacological effects on controlling lipid distribution in dyslipidemia. Mango (*Mangifera indica*), cashew (*Anacardium occidentale*), and sumac (*Rhus coriaria*) are Anacardiaceae family species that people around the world widely consume. These species contain high fiber and saturated fat, which help improve body lipid levels. The literature used in this review was obtained from some databases, including PubMed, Google Scholar, and Science Direct. In this review, 15 species of Anacardiaceae will be reviewed for their antidyslipidemic activity in vivo and in vitro experiments for the past10 years. Some of the articles studied the mechanisms of the lowering-lipid profile, but the information remains unclear. Future trials with the study of the molecular mechanisms of those species are fascinating to understand.

Keywords: Anacardiaceae family, Pharmacological effect, Dyslipidemia, Lipid profile

Introduction

Dyslipidemia is one of the most CNCD caused by abnormalities in lipid metabolism resulting from excess intake of trans fats, saturated fats, and cholesterol [1]. This is characterized by an increase in plasma total cholesterol levels, low-density lipoprotein (LDL) and triglyceride levels, and a decrease in high-density lipoprotein (HDL) levels [2]. Abnormalities of these lipid profiles are the main risk factors in the onset of cardiovascular diseases such as atherosclerosis, hypertension, diabetes mellitus, coronary heart disease, and many others [3-5]. Although primary therapies for hyperlipidemia (such as statins) which are inhibitors of cholesterol biosynthesis have become an intervention, it has not demonstrated ideal cholesterol levels in every statin-treated patient, which requires improvement [6].

Studies on the pharmacological activities or therapeutic effects of plant extracts have been carried out [7]. One of them is the exploration of activity to improve the abnormalities of lipid levels in dyslipidemia. Anacardiaceae is a plant family, also known as a cashew family, consisting of 75 genera and over 700 species in the world. These plants are commonly found in tropical regions, consisting of fruiting plants widely consumed or as traditional medicine [8]. Some species of the Anacardiaceae family that are well known in the wider community are *Anacardium occidentale* (cashew), *Mangifera indica* (mango), and *Rhus criteria* (sumac). These species have been reported to have various pharmacological activities, including anti-inflammatory, antioxidant, antimicrobial, and even anti-diabetic [9-12]. In addition, their bioactive compounds and secondary metabolites that contribute to their pharmacological effects have been widely explored, including polyphenolic compounds, mangiferin,

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galoyl, ellagic acid, flavonoid, tocopherol, sterol, saponin, tannin, alkaloid, cardiac glycoside, and steroid [13-16].

Fifteen species of the Anacardiaceae family were selected to be reviewed for their pharmacological effects on controlling the lipid profile of dyslipidemia. Those species are *Anacardium occidentale* [17-21], *Buchanania lanzan* Spreng [22], *Lennea edulis* [23], *Mangifera indica* [24-28], *Pistacia atlantica* [29], *Pistacia khinjuk* [30], *Pistacia lentiscus* [31-33], *Pleiogynium timorense* [34], *Protorhus longifolia* [35], *Rhus coriaria* [36-40], *Rhus mysurensis* Heyne [41], *Rhus verniciflua* [42], *Schinus terebinthifolius* [43], *Semecarpus anacardium* [44, 45], and *Spondias pinnata* [46, 47]. As those species are varied, their substances are different, leading to their variety of pharmacological effects. So in this study, we will describe the differences, and maybe there will be similarities of the pharmacological effects from the species of Anacardiaceae.

In vivo evaluation

26 in vivo experiments of 15 Anacardiaceae family species selected to be reviewed in this article. This review of the in vivo evaluation of the Anacardiaceae family on controlling lipid profile is summarized in **Table 1** below.

Table 1. In Vivo Experiments of Anacardiaceae Family On Lipid Profile

Species	Methods	Plant part	Parameter	Doses	Result	Reference
***Anacardium occidentale* L.**	Cerebral Ischemic Rats Induced by the Occlusion of Right Middle Cerebral Artery	Nuts	TC, TG, LDL, HDL	50 mg/kg BW	↓TC 15,65 mg/dL (16,94%) ↓TG 25,96 mg/dL (36%) ↓LDL 8,73 mg/dL (40%) ↑HDL 11,92 mg/dL (27,5%)	(Wattanathorn *et al*., 2017) [19]
	Dyslipidemic Female Wistar Rats	Nuts	TC, TG, LDL, HDL, VLDL	400 mg/kg BW	↓TC 32,43 mg/dL (34%) ↓TG 3,6 mg/dL (30,77%) ↓LDL 27 mg/dL (37,50%) ↓VLDL 0,9 mg/dL (20%) ↑HDL 2,34 mg/dL (35%)	(Batista *et al*., 2018) [17]
	Atherogenic Diet-Induced Obese Rats	Fruits	TC, TG, LDL, HDL, VLDL	400 mg/kg BW	↓TC 231,44 mg/dL (75,6%) ↓TG 120,35 mg/dL (63,1%) ↓LDL 57,72 mg/dL (75,3%) ↓VLDL 58,65 mg/dL (74%) ↑HDL 7,74 mg/dL (83,59%)	(Jhansyrani *et al*., 2019) [20]
	Dyslipidemic Rats	Nuts	TC, TG, HDL	4000 mg/kg BW	↓TG 40 mg/dL (28,57%) ↑HDL 20 mg/dL (66,67%)	(Dias *et al*., 2019) [18]
***Buchanania lanzan* Spreng**	Streptozotocin-Induced Types I and II Diabetic Rats	Leaves	TC, TG, LDL, HDL	100 mg/kg BW	↓TC 51,34 mg/dL (37%) ↓TG 119,33 mg/dL (56%) ↓LDL 43,14 mg/dL (51%) ↑HDL 15,67 mg/dL (152%)	(Sushma *et al*., 2013) [22]
Lennea edulis	Alloxan-Induced Diabetic Rats	Leaves	TC, TG, LDL, HDL, VLDL	500 mg/kg BW	↓TC 201,5 mg/dL (65%) ↓TG 223 mg/dL (65,7%) ↓LDL 179,23 mg/dL (80%) ↓VLDL 44,6 mg/dL (65,7%) ↑HDL 22,33 mg/dL (126%)	(Banda *et al*., 2018) [23]
Mangifera indica L.	High Cholesterol Diet-Induced Hypercholesterolemic Rats	Leaves	TC and TG	90 mg/kg BW	↓TC 103,5 mg/dL (67%) ↓TG 133,6 mg/dL (63%)	(Gururaj *et al*., 2017) [25]
	Hypercholesterolemic Diet-Induced Dyslipidemic Wistar Rats	Leaves	TC, TG, HDL	400 mg/kg BW	↓TC 100 mg/dL (50%) ↓TG 90 mg/dL (47%)	(Sandoval-Gallegos, 2017) [24]
Pistacia atlantica	Streptozocin-Induced Diabetic Mice	Hulls	TC, TG, LDL, HDL, VLDL	200 mg/kg BW	↓TC 48,2 mg/dL (36%) ↓TG 48,4 mg/dL (39%) ↓LDL 18,9 mg/dL (32%) ↓VLDL 9,7 mg/dL (39%) ↑HDL 3 mg/dL (12%)	(Hosseini *et al*., 2020) [29]
Pistacia khinjuk	High Fat Diet-Induced Hyperlipidemic Rats	Leaves	TC, TG, HDL, LDL	300 mg/kg BW	↓TC 78,6 mg/dL (40,5%) ↓TG 183,4 mg/dL (42,3%) ↓LDL 91,8 mg/dL (57,5%) ↑HDL 38,8 mg/dL (100,9%)	(Kamal *et al*., 2017) [30]
Pistacia lentiscus	Streptozocin-Indiced Diabetic Mice	Mastic gum (resin)	TC, TG, LDL, HDL	20 mg/kg BW	↓TC 18,7 mg/dL (19%) ↓TG 75,4 mg/dL (63%) ↓LDL 15,7 mg/dL (44%) ↑HDL 12,11 mg/dL (32%)	(Georgiadis *et al*., 2013) [31]

	Egg Yolk Diet-Induced Hyperlipidemic Rabbits	Fatty oil	TC, TG, LDL, HDL	2 mL/kg BW	↓TC 2,37 g/L (34,9%) ↓TG 1,69 mg/L (50,75%) ↓LDL 2,20 mg/L (38,06%)	(Djerrou, 2014) [32]
	Alloxan-Induced Diabetic rats	Leaves	TC, TG, LDL, HDL	300 mg/kg BW	↓TC 40 mg/dL (40%) ↓TG 80 mg/dL (66%) ↓LDL 20 mg/dL (60%)	(Cherbal *et al.*, 2017) [33]
Pleiogynium timorense	Hyperlipidemic Diet-Induced Hyperlipidemic Rats	Seeds	TC, TG, LDL, HDL, TL	300 mg/kg BW	↓TC 26,01 mg/dL (24%) ↓TG 31,93 mg/dL (34%) ↓LDL 27,1 mg/dL (48%) ↓TL 103,1 mg/dL (30%) ↑HDL 8,9 mg/dL (45%)	(Said *et al.*, 2018) [34]
	High Cholesterol Diet-Induced Hypercholesterolemic Rats	Fruits	TC and TG	200 mg/kg BW	↓TC 52,62 mg/dL (34.17%) ↓TG 78,64 mg/dL (55.92%)	(Shafiei *et al.*, 2011) [36]
	Dietary *Rhus coriaria* L. Powder Fed Chicken Broiler	Fruits	TC, TG, LDL, HDL, VLDL	10 g/kg diet	↓TC 47 mg/dL (31%) ↓TG 5 mg/dL (9,6%) ↓VLDL 3,4 mg/dL (28%) ↑HDL 7,6 mg/dL (31%)	(Golzadeh *et al.*, 2012) [37]
***Rhus coriaria* L.**	Streptozocidn-Induced Diabetic Type 2	Seeds	TC, TG, LDL, HDL, VLDL	400 mg/kg BW	↓TC 69,7 mg/dL (38%) ↓LDL 61,36 mg/dL (43%) ↓VLDL 12,71 mg/dL (38%)	(Anwer, 2012) [38]
	Nicotinamide-Streptozotocin-Induced Type In Diabetic Male Mice	Seeds	TC, TG, LDL, HDL, VLDL	300 mg/kg BW	↓TC 24,02 mg/dL (28%) ↓TG 29,6 mg/dL (23%) ↓LDL 12,82 mg/dL (73%) ↓VLDL 5,92 mg/dL (23%) ↑HDL 14,89 mg/dL (84%)	(Ahangarpour *et al.*, 2017) [40]
	High Fat Diet-Induced Hepatic Steatosis in Rats	Fruits	TC, TG, LDL, HDL	250 mg/kg BW	↓TC 5,8 mg/dL (7%) ↓TG 47 mg/dL (49%) ↓LDL 9,6 mg/dL (33%) ↑HDL 14,5 mg/dL (43%)	(Pasavei *et al.*, 2018) [39]
***Rhus mysurensis* Heyne**	Streptozotocin Induced Diabetes in Wistar Male Rats	Roots	TC, TG, LDL, HDL	800 mg/kg BB	↓TC 76,87 mg/dL (45,6%) ↓TG 41,73 mg/dL (29,6%) ↓LDL 78,73 mg/dL (65%) ↑HDL 10,08 mg/dL (51,6%)	(Lamba *et al.*, 2014) [41]
Rhus verniciflua	Diet-Induced Hyperlipidemia in Mice	*Rhus verniciflua* Stokes (RVS)	TC, HDL, LDL, Hepatic Cholesterol and Hepatic bile-acids	1000 mg/kg BW	↓TC 30 mg/dL (16,7%) ↓LDL 2 mg/dL (22,2%) ↓Hepatic Cholesterol 10 mg/dL (8,3%) ↑Hepatic bile-acids 75 µmol/g (37,5%)	(Jeong *et al.*, 2015) [42]
Schinus terebinthifolius	Atherogenic Diet-Induced Obese Rats	Fruits	TC, TG, LDL, HDL	50 mg/kg BW	↓TC 40,3 mg/dL (32,4%) ↓TG 37,4 mg/dL (26,8%) ↓LDL 31 mg/dL (41,9%) ↑HDL 4,9 mg/dL (20,6%)	(Feriani *et al.*, 2021) [43]
Semecarpun anacardium	Streptozocin-Induced Type 2 Diabetic Rat Model	Nuts	HDL, LDL, TC, TG	200 mg/kg BW	↓TC 94 mg/dL (42,5%) ↓TG 40 mg/dL (32%) ↓LDL 32 mg/dL (56,1%) ↑HDL 29 mg/dL (138%)	(Khan *et al.*, 2012) [44]
	Hyperlipidemic Wistar Albino Rats	Fruits	TC, TG, VLDL	45 mg/kg BW	↓TC 17 mg/dL (22%) ↓TG 106 mg/dL (60.2%) ↓VLDL 20 mg/dL (56.8%)	(Dwivedi *et al.*, 2018) [45]
Spondias pinnata	Streptozocin-Induced Diabetic Rats	Barks	TC, TG, LDL, HDL, VLDL	1000 mg/kg BW	↓TC 20,36 mg/dL (19,5%) ↓TG 9,37 mg/dL (24,3%) ↓LDL 19,64 mg/dL (25,5%) ↓VLDL 1,98 mg/dL (25,6%) ↑HDL 1,26 mg/dL (6,4%)	(Attanayake *et al.*, 2014) [46]

Alloxan-Induced Hyperglycemic Rats	Fruits	TC, TG, LDL, HDL, VLDL	1000 mg/kg BW	↓TC 7,67 mg/dL (14,7%) ↓TG 34,34 mg/dL (37,5%) ↓LDL 5,67 mg/dL (42,4%) ↓VLDL 6,86 mg/dL (37,4%) ↑HDL 4,86 mg/dL (23,7%)	(Sutradhar *et al.*, 2018) [47]

Notes: ↓ = decrease; ↑ increase
Abbreviations: TC= total cholesterol; TG= triglyceride; LDL= low-density lipoprotein; HDL= high-density lipoprotein; VLDL= very-low-density lipoprotein; TL = Total Lipid

Lipid profile

All species of the Anacardiaceae family possess promising antidyslipidemic activity characterized by improvement in lipid profile. Abnormalities of lipid profile including TC, TG, LDL, VLDL, and HDL are signs of dyslipidemia. It can be seen in **Table 1**. that most Anacardiaceae species exhibit the lowering effect of TC, TG, LDL, VLDL levels, and higher levels of HDL. Therefore, species from the Anacardiaceae family can cure abnormal lipid profiles in dyslipidemia, as described below.

Total cholesterol (TC)

Total cholesterol is the total amount of cholesterol in the body, including LDL and HDL. The high amount of cholesterol resulting in a high risk of CVD, particularly atherosclerosis. High cholesterol can accumulate fat in blood cells, decrease blood flow, and caused heart attack or stroke [48]. Cholesterol-lowering agent needed to prevent morbidity and mortality of cardiovascular disease (CVD). As shown in **Table 1**, all species of Anacardiaceae have a cholesterol-lowering effect in an animal model with a percent reduction of 7%-75%. Meanwhile, the percent reduction of a potent agent of lowering cholesterol (statin) is 29-40% [49]. 19 of 26 in vivo experiments, including ten species of Anacardiaceae, show their cholesterol-lowering effects above 29% means these are comparable to statin. It could be concluded that these Anacardiaceae species potentially be the new cholesterol-lowering agent.

Fruits extract of *Anacardium occidentale* show highest percent reduction of total cholesterol with 75,6% (231,44 mg/dL) at 400 mg/kg BW dose [20]. The main bioactive compound of *Anacardium occidentale* is a polyunsaturated fatty acid that contributes to lipid metabolisms. 9,12-octadecadienoic acid, 9,12-octadecadienoyl chloride, and 15-hydroxy-pentadecanoic acid are reported to be in this species. Potential mechanisms of polyunsaturated fatty acid in lowering cholesterol are by modifying the secretion of TG and cholesterol esterase, also increasing function of LDL receptor. These prevent the development of atherosclerosis, although the HDL level is low due to poor production and high catabolism of Apo A-l [50]. The molecular experiment of this species is still lacking. Further trial for the precise mechanism of action should be needed.

Triglyceride (TG)

Triglyceride (TG) is an ester derived from glycerol and three fatty acids. It is the major component of body fat in humans, along with vegetable fat. Plasma TGs are formed by exogenous, which is from the diet, and endogenous, which is from the liver carried in VLDL particles. It is correlated with several in vivo studies that are used a high-fat diet to induce dyslipidemia resulting in high TG levels [45]. High TG levels cause hypertriglyceridemia that concluded in dyslipidemia. TG levels are a secondary target for dyslipidemia therapy. Several prospective epidemiological studies have indicated elevated TG levels correlated with a high risk of heart disease [51]. Based on **Table 1**, the percent reduction of lipid profile by 15 species of Anacardiaceae family show varied with 9-66%. Compared to fibrate as a potent lipid-lowering agent that possesses reduction of TG levels 40-60% [52], 8 of 16 Anacardiaceae species elicit a percent reduction of more than 40%. This finding shows that Anacardiaceae species have the lipid-lowering effect comparable to potent agents, making it possible to improve the previous triglyceride-lowering agent with some side effects.

Among all the species, the Fatty oil of *Pistacia lentiscus* exhibit superior TG reduction with 66% and 80 mg/dL. This fatty oil reported as monounsaturated fatty oil, which is consists of high oleic acid. Monounsaturated fatty acid (MUFA) possesses lipid-lowering activity that leads to CVD protection [53]. Besides that, the fatty oil of *Pistacia lentiscus* consists of palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid, gadoleic acid, saturated fatty acid (SFA), monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA). Djerrou *et al.*, 2014) reported that a good PUFA/SFA ratio contributes to the lowering effect of this fatty oil. It could be accomplished by α-tocopherol and squalene that consist in the unsaponifiable fraction [32].

Low-density lipoprotein (LDL)

Low-density lipoprotein (LDL) is an influential lipoproteins group that delivers all fat molecules around the body to cells. LDL is oxidized when it is defected by free radicals in the arterial walls and leads to atherosclerosis [54]. LDLs are small dense fat molecules consist of high cholesterol esters that are formed by transporting the TG. This process involves a lipoprotein lipase enzyme (LPL) that carries TG from VLDL. Elevated LDL levels are indicated as familial hypercholesterolemia that causes the development of atherosclerosis CVD [55]. Fifteen species of Anacardiaceae reported has LDL-lowering activities with a percent reduction of 22-80%. This effect is comparable to a statin, which reduces LDL levels up to 60% [56]. Moreover, five species exhibit a percent reduction of 60% and more which are *Anacardium occidentale* (fruit), *Lennea edulis* (leave), *Pistacia lentiscus* (leave), *Rhus coriaria* L. (seed), and *Rhus mysurensis* Heyne (root) [20, 23, 33, 40, 41]. With this practical LDL-lowering effect, Anacardiaceae species could be a future better agent of controlling lipid profile in dyslipidemia.

Leaves extract of *Lennea edulis* has the highest percent reduction of LDL levels in an animal study with 80% and 179,23 mg/dL. These lipid-lowering effects could be associated with their secondary metabolites content. As reported by Banda *et al.*, 2018, *Lennea edulis* contains flavonoids, saponins, tannins, alkaloids, cardiac glycosides, and steroids. Possible mechanisms of its effect are due to saponin content that previously reported inhibit the absorption of cholesterol and induce the secretion of cholesterol by excreting the bile acids [57]. Future trials to examine the molecular mechanisms of these effects should be needed.

Very-low density lipoprotein (VLDL)

VLDL is synthesized in the liver and released into the bloodstream carrying TG to body tissues. VLDL and LDL can cause plaque that is formed of fat, cholesterol, calcium, and other particles in the blood. The accumulation of fat results in reduced oxygen in the blood, leading to heart disease, especially in the arteries [58]. That means high levels of VLDL are abnormalities of a lipid profile that has to be cured. In the present study of Anacardiaceae family species, as shown in **Table 1**, 6 of 15 species possess a lowering effect of VLDL level with a percent reduction of 20-70%. Those species are *Anacardium occidentale* (nut and fruit), *Lennea edulis* (leave), *Pistacia Atlantica*, *Rhus coriaria* L. (seed), and *Spondias pinnata* (bark and fruit) [17, 20, 23, 29, 38, 40, 46, 47]. Atorvastatin as an antidyslipidemic agent has a percent reduction of VLDL levels as much as 60% [20] making these lipid-lowering effects of these species is comparable to atorvastatin.

Sumac (*Anacardium occidentale*) shows tremendous potential to be an alternative antidyslipidemic to improve the previous antidyslipidemic agent that still has disadvantage effects with a 74% reduction of VLDL levels. As reported by Dwivedi *et al.*, 2018, the possible mechanism of the VLDL-lowering effect of sumac is by inhibiting the absorption of exogenous fat. In this process, there are two enzymes involved: pancreatic cholesterol esterase and acyl Co-A cholesterol acyltransferase enzyme (ACAT) Furthermore, sumac may inhibit these enzymes to elicits its lipid-lowering effect. Besides that, sumac is reported to contain numerous secondary metabolites that are ω-7 fatty acids, steroids, flavonoids, and polyphenolic compounds [59]. These compounds may contribute to the sumac lipid-lowering effect by several mechanisms. However, the precise molecular mechanisms of sumac still lack future trials to determine the mechanisms of action in this species that could be needed.

High-density lipoprotein (HDL)

HDL is composed of high protein and be the most heterogeneous lipoprotein. In addition, protein is the essential part of HDL particles that determine their function and structure. HDL plays a role in cholesterol efflux from peripheral cells and transports cholesterol to the liver. HDL level is used to calculate cardiovascular risk and is inversely associated with CVD and coronary death, independently from other traditional risk factors [60]. In dyslipidemia, HDL levels are lower than the normal range of a healthy person. Therefore, elevating HDL is the key to improve the abnormalities lipid profile of dyslipidemia. All Anacardiaceae species, as described in **Table 1**, except *Mangifera indica* and *Rhus verniciflua* show their effects on increasing the HDL levels with percent increasing 12-152% or almost twofold of normal levels. Compared to the potent agent, niacin, which can increase HDL level up to 20% [61], species Anacardiaceae show promising superior effects. It could be the new candidate for improvement antidyslipidemic, mainly focused on elevating HDL levels.

The highest increase is found in *Pistacia atlantica* extract with 152%. It has been reported that the primary chemical compound of this species is a flavonoid and phenolic compound. Phenolic compounds are well known to have inhibitory activity of HMG-CoA reductase (HMGR), the rate-limiting enzymes of cholesterol biosynthesis. HMGR is responsible for converting HMG-CoA to mevalonate, clear this enzyme is the initial precursor of cholesterol biosynthesis [62]. Inhibition of HMG-CoA reductase leads to an increase of peroxisome proliferator-activated receptor alpha (PPARα) expression and increases Apolipoprotein A-1 (Apo A-1) synthesis in the liver. This results in an enhancing effect on the formation of HDL precursors [63].

In vitro evaluation

Some of in vitro evaluation of anacardiaceae family species are described in **Table 2** below. In this review, we explored the methods, result of study, and the mechanisms of action of these species.

Table 2. In Vitro Experiments of Anacardiaceae Family On Lipid Profile

Species	Part of Plant	Methods	Results	Mechanism of Action	Reference
***Anacardium occidentale* L.**	Leaves	An in-cell western assay using Hep G2 cell line	↑the concentration of Apo A-1, LCAT, SR-B1, ABCA1 and HL	involve in reverse cholesterol transport process to reduce cholesterol metabolism in Hep G2 cell	(Hasan *et al.*, 2015) [21]
***Mangifera indica* Linn.**	Leaves	AMPK and PI3K/AKT signaling pathways	↑AMPK ↓ACC (2.8-fold) ↓HSL (1.6-fold) ↓FAS (1.8-fold) ↓PPAR-c (4.0-fold).	up-regulated AMPK and down-regulated expression of adipogenic genes (ACC, FAS, HSL)	(Zhang *et al.*, 2013) [26]
	Leaves	Cholesterol esterase inhibition	IC50 0.86 µg/ml	inhibit the absorption of dietary cholesterol esters in the intestinal lumen	(Gururaja *et al.*, 2015) [25]

	Leaves	Adipogenic differentiation using 3T3-L1 cells	inhibit lipid accumulation	Increased HO-1 and PPAR-α expression	(Sferrazzo *et al*., 2019) [27]
Protorhus longifolia	Stem bark	Pancreatic lipase and cholesterol esterase inhibitory assay	IC50 = 0.04 – 0.31 mg/dL Percentage of adsorption ability on bile acid = ±60% ↓ lipid accumulation ±25%	Inhibited lipid digestive enzymes and lipolysis, and binding bile acid	(Mosa *et al*., 2014) [35]

Notes: ↓ = decrease; ↑ increase

Abbreviations: Apo A-1 = apolipoprotein A-1; LCAT = lecithin cholesteryl acyl transferase; SR-B1 = scavenger receptor class B type 1; ABCA-1 = ATP binding cassette transporter A1; HL = hepatic lipase; AMPK = AMP-activated protein kinase; ACC= acetyl-CoA carboxylase; HSL= hormone sensitive lipase; FAS = fatty acid synthase; PPAR-γ= peroxisome proliferator-activated receptor γ; HO-1 = heme oxygenase-1

Reverse cholesterol transport (RCT) pathway

RCT is a mechanism of transporting the excess cholesterols from peripheral tissues back to the liver when cells are not used. HDL transports cholesterol from atherosclerotic plaques or other lipids back to the liver to be excreted within the RCT process. The cholesterol is ingested into HDL particles, esterified with a long-chain fatty acid by LCAT. Afterward, cholesterol is taken up within the liver and excreted in bile. This RCT is directed by a few proteins and enzymes such as Apo A-I, LCAT, SR-B1, HL, and LDL receptor (LDLR) [64]. As can be seen in **Table 2**, leaves extract of *Anacardium occidentale* reported elicits elevating the concentration of molecules that contribute in RCT pathway including Apo A-1, LCAT, SRB-1 ABCA-1, and HL [21]. Apo A-I is essential for nascent HDL formation, while high secretion of Apo A-1 is desired to increase the RCT. Other than that, LDLR correlates with HL, which is HL activates VLDL to form into LDL then undertaken by LDLR from plasma. Two more molecules involved in the RCT pathway are SRB-1, which removes cholesteryl esterase (CE) and carries out free cholesterol to be broken down in the liver, and ABCA-1, which is responsible for decreasing plaque atheroma formation [65]. These results suggested that *Anacardium occidentale* potentially as anticholesterol by increasing molecules involving in the RCT pathway.

AMPK and PI3K/AKT signaling pathways

TG metabolism involves various signaling pathways, including free fatty acids (FFA), phosphoinositide 3-kinases (PI3K), PPAR, adipocytokines, mitogen-activated protein kinase (MAPK), and AMP-activated protein kinase (AMPK) [66]. As demonstrated in **Table 2**, leaves extract of *Mangifera indica* significantly lowered the adipogenic genes expression, such as ACC, HSL, and FAS. AMPK activation via suppression of SREBP-1c and inhibition of enzymes involved in TG synthesis has been found in several previous studies [67]. This indicates a potential involvement of PI3 K/AKT and AMPK signaling pathway in the mechanism of this action.

Cholesterol esterase inhibitor

Cholesterol esterase works to hydrolyze long-chain fatty acid esters into cholesterol and fatty acids, which are then excreted in the intestinal lumen. This process is carried out because esters from cholesterol cannot be absorbed directly by intestinal epithelial cells, so they must be hydrolyzed into simpler molecules. If the enzyme cholesterol esterase is inhibited, cholesterol esters from food cannot be absorbed [68]. Gururaja *et al*., 2015 reported that leaves extract of *Mangifera indica* has an inhibitory activity of cholesterol esterase; thus, this extract exhibits hypolipidemic activity. In this study, a bioactive compound isolated from *Mangifera indica* is 3 β-taraxerol that showed cholesterol esterase inhibition with IC50 8,7 μg/mL [25]. 3 β-taraxerol is a sterol that competes with cholesterol within the mixed micelles, required for cholesterol absorption by the small intestine. Moreover, it leads to decreased cholesterol absorption from diet or even bile acid resulting in reduced cholesterol levels in blood [28].

Pancreatic lipase inhibitor

Enzymes involved in lipid digestion include pancreatic lipase and cholesterol esterase. If these enzymes are inhibited, the absorption of lipids from exogenous (food) will be reduced. As well as the inhibition of adipogenesis and lipolysis, through the inhibition of lipid-digesting enzymes is an effective means of treating hyperlipidemia and other related diseases [69]. *Protorhus longifolia* has been reported to contain triterpene, a bioactive compound that possesses many therapeutic effects. The triterpene isolated from this species is 3β-hydroxylanosta9,24-dien-21-oic acid and methyl-3β-hydroxylanosta-9,24-dien-21-oate show inhibitory activity against pancreatic lipase, CE, and HSL with IC50 0.04-0.31 mg/mL as presented in **Table 1**. These IC50 values are comparable to those of the positive controls used. Inhibitors of HSL are essential to drug targets in preventing hyperlipidemia and consequent peripheral insulin resistance [22]. Based on the results of this in vitro experiment, the triterpenes of *Protorhus longifolia* have inhibitory activity against pancreatic lipase and HSL. Therefore, it can be concluded that the two triterpenes have the potential to treat dyslipidemia through inhibition of exogenous fat and also lipolysis.

Conclusion

Various studies in animal (in vivo) and cell (in vitro) of 16 species of Anacardiaceae family selected in this review demonstrate their ability to improve the abnormalities lipid profile. Although their effects are varied, they depend on bioactive compounds that play a primary role in each activity. The polyphenolic compound of these species seems the most bioactive compound that exhibits

many beneficial effects and possesses possible mechanisms of action. Four molecular mechanisms that have been reported to contribute to the antidyslipidemic activity of Anacardiaceae family species are inhibitory cholesterol esterase and pancreatic lipase, reverse cholesterol transport pathway, and AMPK PI3K/AKT signaling pathways. The lipid-lowering effect of improving lipid profile in dyslipidemia of these species shows a potent effect comparable to antidyslipidemic drugs such as statins, fibrates, and niacin. Therefore, the Anacardiaceae family species can be new drug candidates in the treatment of dyslipidemia.

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