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Medicinal plants as potential anti-cholesterol agents: a narrative review of *in vivo, in vitro,* and *in silico* evidence

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ABSTRACT

Background: Hypercholesterolaemia is a major cardiovascular risk factor commonly managed with statins, which are frequently associated with hepatotoxicity, myopathy, and new-onset diabetes mellitus, driving interest in medicinal plants as natural alternatives.

Objective: This review aimed to identify medicinal plants with demonstrated or predicted anti-cholesterol activity, specifying plant species, plant parts, and evidence from *in vivo*, *in vitro*, and *in silico* studies.

Methods: A narrative literature review was conducted following PRISMA 2020 guidelines. Original articles published between 2014 and 2024 were retrieved from Google Scholar, Google, and PubMed. Review articles and studies unavailable in full text were excluded.

Results: Nineteen articles met the eligibility criteria. Fourteen medicinal plants demonstrated cholesterol-lowering activity in *in vivo* and *in vitro* studies. Five plants were assessed *in silico*; quercetin-type flavonoids from karamunting, sweet orange, and soursop showed binding free energies more favourable than statin controls against HMG-CoA reductase, while butterfly pea and water clover compounds did not surpass their controls.

Conclusion: Extracts from kirinyuh, ceremai, and ketapang achieved notable cholesterol reductions at low effective doses in animal models. Green kiwi fruit extract showed the greatest *in vitro* potency (EC50 = 7.3 ppm). *In silico* findings are preliminary and require experimental validation. Further research should isolate active compounds and evaluate efficacy through clinical studies in humans.

Keywords: Hypercholesterolaemia; Medicinal plants; HMG-CoA reductase; *In vivo*; *In vitro*; *In silico*

Introduction

Cholesterol is a lipid widely distributed in human tissues and is essential for maintaining cell membrane integrity, participating in key metabolic processes, and serving as a precursor for the synthesis of steroid hormones and fat-soluble vitamins. However, when present in excessive amounts, cholesterol poses significant health risks. Elevated blood cholesterol levels, termed hypercholesterolaemia, constitute a major risk factor for metabolic disorders and cardiovascular diseases [1]. Hypercholesterolaemia is characterised by elevated levels of total cholesterol, low-density lipoprotein (LDL), and triglycerides, each of which may contribute to serious clinical complications [2].

The global burden of hypercholesterolaemia is substantial. In 2019, the condition affected approximately 45% of the adult population worldwide, while Southeast Asia reported a prevalence of approximately 30% among adults [3]. In Indonesia, data from the 2018 Basic Health Research (Riskesdas) indicated that 7.6% of individuals aged 15 years and older, representing approximately 20 million people, had total cholesterol levels meeting the criteria for hypercholesterolaemia [4]. These figures are consistent with broader global trends documented by the NCD Risk

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Factor Collaboration, which reported a repositioning of the epicentre of raised cholesterol burden toward low- and middle-income countries [5].

Cholesterol biosynthesis proceeds through the mevalonate pathway, in which the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyses the rate-limiting conversion of HMG-CoA to mevalonate, which is subsequently converted to cholesterol. Inhibition of this enzyme therefore represents the primary pharmacological strategy for reducing endogenous cholesterol production [6]. Synthetic statin drugs are currently the first-line treatment for hypercholesterolaemia owing to their efficacy as competitive inhibitors of HMG-CoA reductase [1]. However, statin therapy is frequently associated with adverse effects, including hepatotoxicity, myopathy, and a dose-dependent increase in the risk of new-onset diabetes mellitus [7,8].

These limitations have driven growing interest in medicinal plants as natural alternatives for the management of hypercholesterolaemia. Medicinal plants are valued for their diverse bioactive secondary metabolites, including flavonoids, saponins, tannins, and triterpenoids, which have been reported to exert cholesterol-lowering effects through various mechanisms [9]. Multiple plant parts, including fruits, leaves, stems, roots, and seeds, are used in traditional medicine and are believed to contribute to the alleviation of a range of conditions [10].

Although numerous studies have investigated the anti-cholesterol activity of medicinal plants, the available evidence remains dispersed across different publications and experimental methodologies. Previous studies have generally focused on a single plant species or employed a single experimental approach, such as exclusively *in vitro* or *in vivo* methods. Consequently, a review that integrates evidence from multiple complementary approaches, namely *in vivo*, *in vitro*, and *in silico* studies, is currently lacking. Therefore, this review aims to identify medicinal plants with demonstrated or predicted anti-cholesterol activity, encompassing information on plant species, plant parts examined, and supporting evidence from *in vivo*, *in vitro*, and *in silico* studies. By synthesising evidence across these three experimental approaches, this review seeks to provide a more comprehensive understanding of the potential of medicinal plants as plant-based therapies for the management of hypercholesterolaemia.

Methods

Study design

This study employed a narrative literature review methodology to systematically trace, evaluate, and synthesise published research on the anti-cholesterol activity of medicinal plants through *in vivo*, *in vitro*, and *in silico* approaches. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [11].

Eligibility criteria

Articles were screened for inclusion and exclusion based on pre-specified eligibility criteria. The inclusion criteria were as follows: (1) original research articles published between January 2014 and December 2024; (2) articles written in Indonesian or English; (3) articles available in full text; and (4) articles reporting cholesterol-lowering activity of medicinal plants through *in vivo*, *in vitro*, or *in silico* experimental methods. Articles were excluded if they were: (1) review articles, systematic reviews, or meta-analyses; (2) not available in full text; or (3) published outside the specified timeframe. The eligibility criteria were established prior to the search to minimise selection bias [12].

Information sources and search strategy

A systematic literature search was conducted across three electronic databases: Google Scholar, Google, and PubMed. The search was performed from January 2014 to December 2024. The following search terms were used, either individually or in combination using Boolean operators: "medicinal plants," "*in vivo*," "*in vitro*," "*in silico*," "anti-cholesterol activity," "hypercholesterolaemia," and "HMG-CoA reductase inhibitor." Searches were conducted in both English and Indonesian to capture relevant literature from both international and regional sources.

Study selection

The titles and abstracts of all retrieved articles were screened independently against the eligibility criteria. Full-text articles were then assessed for final inclusion. The study selection process is presented as a flow diagram adapted from the PRISMA 2020 statement (Figure 1) [11].

Data extraction and synthesis

Data were extracted from each included article using a standardised extraction framework. For *in vivo* studies, extracted data included the plant species, plant part used, animal model, method of hypercholesterolaemia induction, effective dose, and outcome measure. For *in vitro* studies, data extracted included the plant species, plant part, assay method, and EC50 value. For *in silico* studies, data extracted included the plant species, target protein, docking software, tested compounds with their binding free energies, and comparison with the positive control. Extracted data were synthesised narratively, comparing the anti-cholesterol efficacy of medicinal plants across each experimental approach [12].

Results

The systematic literature search across Google Scholar, Google, and PubMed identified a total of 19 original research articles that met all pre-specified eligibility criteria. These articles collectively report the cholesterol-lowering activity of medicinal plants through three experimental approaches: 10 articles reporting *in vivo* studies in animal models, 4 articles describing *in vitro* activity assays, and 5 articles employing *in silico* molecular docking analyses. The selection process is summarised in Figure 1. Results of *in vivo*, *in vitro*, and *in silico* studies are presented in Tables 1, 2, and 3, respectively.

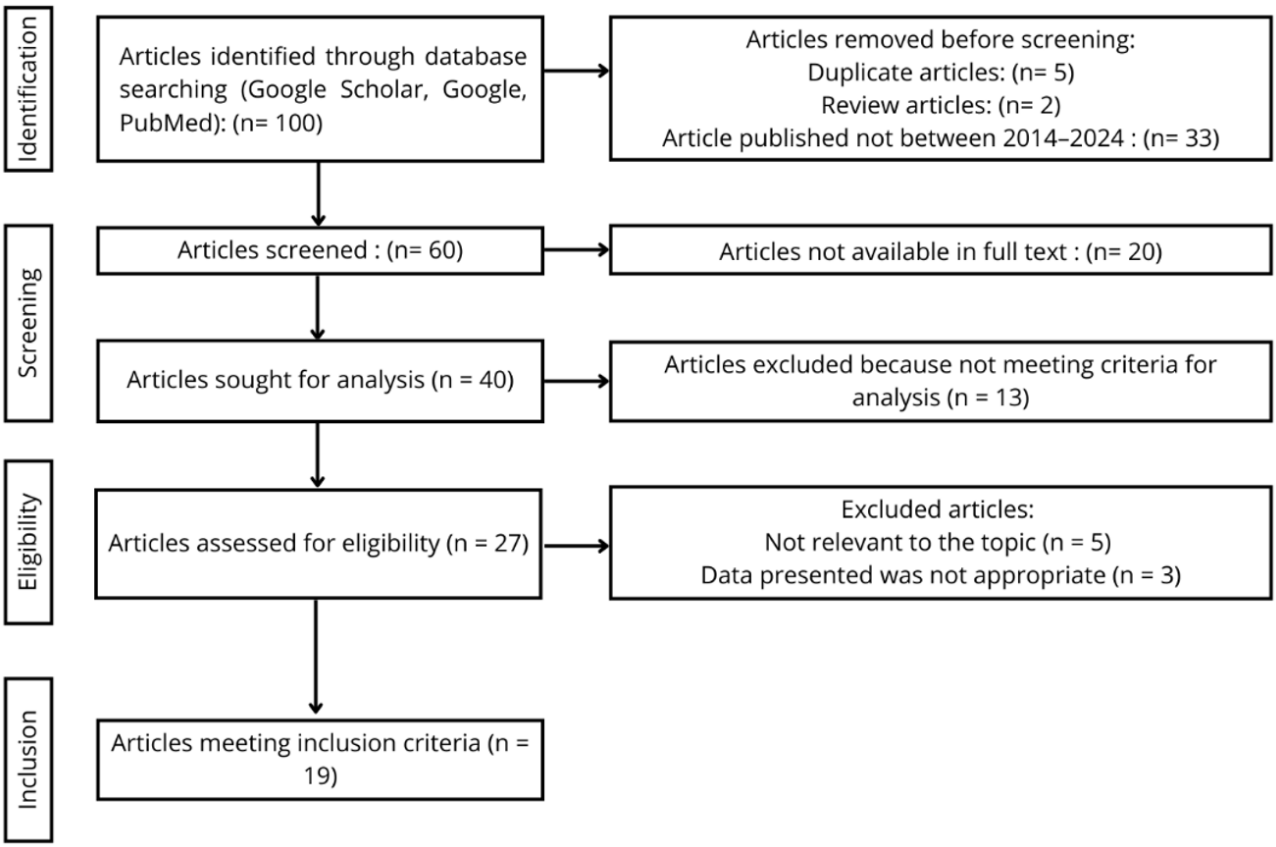

Figure 1. Flowchart of the literature selection process for the review

Table 1. *In vivo* studies of anti-cholesterol activity of medicinal plants

Plant name (scientific name)	Plant part	Effective dose	Key findings	Ref.
Kirinyuh (*Chromolaena odorata* L.)	Leaves	60 mg/kg BW	Cholesterol in male Wistar rats decreased from 60.86 to 30.03 mg/dL; no significant difference from simvastatin ($p > 0.05$).	[13]
Notika (*Archboldiodendron calosericeum* Kobuski)	Leaves	300 mg/kg BW	Total cholesterol reduced by 85.33 mg/dL in male Wistar rats; no significant difference from simvastatin ($p = 0.687$).	[14]
Ketapang (*Terminalia catappa* L.)	Leaves	120 mg/kg BW	Total cholesterol decreased by 59.02% in hypercholesterolaemic Syrian hamsters; atorvastatin achieved 68.74% at same dose.	[15]
Pumpkin (*Cucurbita moschata* Duch.)	Leaves	200 mg/kg BW	Total cholesterol reduced to 103.80 ± 1.92 mg/dL; significantly lower than negative control ($p < 0.05$) and comparable to simvastatin (103.20 ± 1.43 mg/dL).	[16]
Coriander (*Coriandrum sativum* L.)	Seeds	900 mg/kg BW	Mean cholesterol reduction of 9.33 mg/dL in male Wistar rats following one week of treatment.	[17]
Moringa (*Moringa oleifera* Lam.)	Leaves	160 mg/kg BW (= 32 mg/200 g BW)	Cholesterol in male Wistar rats reduced to 74.4 mg/dL; efficacy comparable to simvastatin.	[18]
Soursop (*Annona muricata* L.)	Leaves	150 mg/kg BW	Cholesterol reduced to 161.4 ± 32.30 mg/dL; significantly different from negative control ($p < 0.05$) and comparable to simvastatin.	[19]
Dayak onion (*Eleutherine americana* Merr.)	Tuber	200 mg/kg BW	Cholesterol decreased by 53.25 ± 5.61 mg/dL; reduction not statistically significant ($p = 0.158$).	[20]
Mangkokan (*Polyscias scutellaria* (Burm.f.) Fosberg)	Bark	900 mg/kg BW	Total cholesterol reduced to 122.20 mg/dL; no significant difference from simvastatin ($p = 0.878$).	[21]
Ceremai (*Phyllanthus acidus* (L.) Skeels)	Leaves	100 mg/kg BW	Cholesterol decreased from 349.2 to 180.0 mg/dL; no significant difference from simvastatin ($p > 0.05$).	[22]

BW = body weight; LDL = low-density lipoprotein; Na-CMC = sodium carboxymethylcellulose.

Table 2. *In vitro* studies of anti-cholesterol activity of medicinal plants

Plant name (scientific name)	Plant part	Method	Wavelength; time	EC_{50} value	Ref.
Green kiwi (*Actinidia deliciosa* (A.Chev.) C.F.Liang & A.R.Ferguson)	Fruit	Liebermann-Burchard assay; UV-Vis spectrophotometry	668 nm; 15 min	7.3 ppm (CV = 1.12%)	[23]
Dutch teak (*Guazuma ulmifolia* Lam.)	Leaves	Liebermann-Burchard assay; UV-Vis spectrophotometry	326 nm; 15 min	498 ppm	[24]
Kale (*Brassica oleracea* var. *acephala* DC)	Leaves	Liebermann-Burchard assay; UV-Vis spectrophotometry	668.5 nm; 12 min	32.350 ppm	[25]
Cucumber (*Cucumis sativus* L.)	Peel	Liebermann-Burchard assay; UV-Vis spectrophotometry	665 nm; 15 min	122.04 ppm	[26]

EC50 = half-maximal effective concentration; UV-Vis = ultraviolet-visible spectrophotometry.

Table 3. *In silico* studies of anti-cholesterol activity of medicinal plants

Plant (scientific name)	Software	PDB ID	Tested compounds and binding free energy (kcal/mol)	Positive control and binding free energy (kcal/mol)	Ref.
Karamunting (*Rhodomyrtus tomentosa* (Aiton) Hassk.)	AutoDock Vina	1DQ8	Quercetin 7,4'-diglucoside: −11.4 kcal/mol Myricetin: −10.0 Vitexin: −9.9 Dihydromyricetin: −9.6 Quercetin: −9.4 Kaempferol: −9.2 *All compounds surpassed positive control.*	Simvastatin: −8.8 kcal/mol	[27]
Butterfly pea (*Clitorea ternatea* L.)	YASARA	1HW9	Phloretin: −64.05 kcal/mol Trifolin: −59.24 Trigonelline: −52.76 *All compounds weaker than positive control.†*	Atorvastatin: −72.84 kcal/mol	[28]
Sweet orange (*Citrus sinensis* (L.) Osbeck)	AutoDock Tools	1HWK	Tamarixetin: −19.24 kcal/mol Quercetin-3-O-α-D-arabinofuranoside: −10.67 *Tamarixetin surpassed control; quercetin-3-O-α-D-arabinofuranoside did not.*	Atorvastatin: −16.73 kcal/mol	[29]
Water clover (*Marsilea crenata* C.Presl)	AutoDock Vina	1DQ8	Phytol: −6.37 kcal/mol *Weaker than positive control.†*	Pravastatin: −7.13 kcal/mol	[30]
Soursop (*Annona muricata* L.)	AutoDock 4.0 (web-based)	1HW9	Quercetin 3-O-neohesperidoside: −9.56 kcal/mol Rutin: −9.22 Quercetin: −6.53 Chlorogenic acid: −5.97 Catechin: −5.91 *All compounds surpassed positive control.*	Simvastatin: −4.99 kcal/mol	[31]

† Binding free energies less negative than positive control, indicating weaker predicted inhibitory activity. All studies targeted HMG-CoA reductase. Direct comparison across studies is not appropriate due to differences in docking software and PDB structures. PDB = Protein Data Bank.

Discussion

Plant parts used as anti-cholesterol agents

The data in Tables 1 and 2 show that 14 medicinal plants exhibited cholesterol-lowering activity in *in vivo* and *in vitro* studies. Leaves are the most frequently used plant part (nine species), while bark, seeds, fruit, peel, and tubers are each represented by a single species. These findings suggest that leaves are the most extensively explored plant material in the development of herbal therapies for cholesterol management. This is likely attributable to their ease of harvest, year-round availability, and widespread use in traditional herbal preparations, including decoctions [10].

In vivo study of the anti-cholesterol activity of medicinal plants

In vivo anti-cholesterol studies were conducted using multiple groups of test animals designated as negative control, positive control, and treatment groups receiving plant extracts at varying doses [13–22]. The animal models employed included male Wistar rats, male mice, and Syrian hamsters. Male animals were preferentially selected owing to their more consistent pharmacokinetic profiles and the absence of oestrogen-related hormonal fluctuations that could confound results [33]. White rats (*Rattus norvegicus*) were the most commonly used model, reflecting their established

genetic and physiological similarity to humans, which facilitates the translation of experimental findings [33].

Among the *in vivo* studies reviewed, kirinyuh leaf extract (*Chromolaena odorata* L.) produced notable cholesterol reduction at 60 mg/kg BW, comparable to simvastatin ($p > 0.05$) [13]. Notika leaf extract at 300 mg/kg BW reduced total cholesterol by 85.33 mg/dL, with no significant difference from simvastatin [14]. Ketapang leaf extract at 120 mg/kg BW produced a 59.02% reduction in total cholesterol in hypercholesterolaemic hamsters [15]. Pumpkin leaf extract at 200 mg/kg BW reduced total cholesterol to 103.80 ± 1.92 mg/dL, significantly lower than the negative control ($p < 0.05$) and comparable to simvastatin [16]. Coriander seed infusion at 900 mg/kg BW achieved a mean reduction of 9.33 mg/dL [17], while moringa leaf extract at 160 mg/kg BW reduced cholesterol to 74.4 mg/dL, comparable to simvastatin [18]. Soursop leaf extract at 150 mg/kg BW reduced cholesterol to 161.4 ± 32.30 mg/dL, significantly different from the negative control ($p < 0.05$) [19]. Dayak onion tuber extract at 200 mg/kg BW produced a mean reduction of 53.25 ± 5.61 mg/dL, though not statistically significant ($p = 0.158$) [20]. Mangkokan bark extract at 900 mg/kg BW reduced total cholesterol to 122.20 mg/dL, comparable to simvastatin ($p = 0.878$) [21], and ceremai leaf extract at 100 mg/kg BW reduced cholesterol from 349.2 to 180.0 mg/dL, comparably to simvastatin ($p > 0.05$) [22].

It is notable that kirinyuh, ceremai, and ketapang achieved significant cholesterol reductions at relatively low effective doses of 60, 100, and 120 mg/kg BW, respectively, suggesting a potentially higher potency of their active constituents. However, direct cross-study comparisons of potency must be interpreted with caution, as the included studies employed heterogeneous animal models, induction methods, extract preparations, and dosing protocols. Furthermore, most studies measured total cholesterol without exploring LDL, HDL, or triglyceride fractions in detail, nor the underlying molecular mechanisms. Future research should focus on isolating and characterising the specific bioactive compounds, elucidating their mechanisms of action, and conducting well-designed clinical studies to evaluate safety and efficacy in humans.

In vitro study of the anti-cholesterol activity of medicinal plants

In vitro anti-cholesterol activity was evaluated using the Liebermann-Burchard colorimetric assay and EC50 determination, as shown in Table 2. Green kiwi fruit ethanol extract demonstrated the strongest activity with an EC_{50} of 7.3 ppm [23], followed by kale leaf extract (EC_{50} = 32.350 ppm) [25], cucumber peel extract (EC_{50} = 122.04 ppm) [26], and Dutch teak leaf extract (EC_{50} = 498 ppm) [24].

The anti-cholesterol activity of these extracts is attributable to their secondary metabolite profiles, particularly flavonoids, saponins, tannins, and triterpenoids. Flavonoids exert dual cholesterol-lowering mechanisms: inhibition of HMG-CoA reductase [6] and upregulation of LDL receptor (LDLR) expression, promoting hepatic endocytosis of LDL particles [32]. Saponins modulate cholesterol homeostasis through complex formation with cholesterol in the intestinal lumen and regulation of cholesterol metabolism [34]. Triterpenoids exhibit hypocholesterolaemic activity by inhibiting cholesterol esterase and HMG-CoA reductase and by stimulating LDLR-mediated LDL uptake in hepatocytes [35]. Tannins, particularly procyanidins, also inhibit cholesterol esterase activity, reducing cholesterol absorption [36].

In vitro assays provide only a preliminary indication of cholesterol-lowering potential and do not replicate biological complexity *in vivo*. Further studies are required to isolate specific active compounds and validate efficacy through *in vivo* experiments and clinical trials.

In silico study of the anti-cholesterol activity of medicinal plants

Molecular docking analyses evaluated a total of 16 compounds from five medicinal plants against HMG-CoA reductase (Table 3). Binding free energy measures the strength of predicted ligand-protein interaction; more negative values indicate stronger binding [37]. Among compounds from karamunting (*Rhodomyrtus tomentosa*), all six flavonoids tested exhibited binding free energies more negative than simvastatin (-8.8 kcal/mol), with quercetin 7,4'-diglucoside showing the most favourable interaction at -11.4 kcal/mol, followed by myricetin (-10.0 kcal/mol), vitexin (-9.9 kcal/mol), dihydromyricetin (-9.6 kcal/mol), quercetin (-9.4 kcal/mol), and kaempferol (-9.2 kcal/mol) [27]. From sweet orange (*Citrus sinensis*), tamarixetin (-19.24 kcal/mol) surpassed atorvastatin (-16.73 kcal/mol), whereas quercetin-3-O-α-D-arabinofuranoside (-10.67 kcal/mol) did not [29]. All five compounds from soursop (*Annona muricata* L.) surpassed simvastatin (-4.99 kcal/mol), with quercetin 3-O-neohesperidoside achieving the

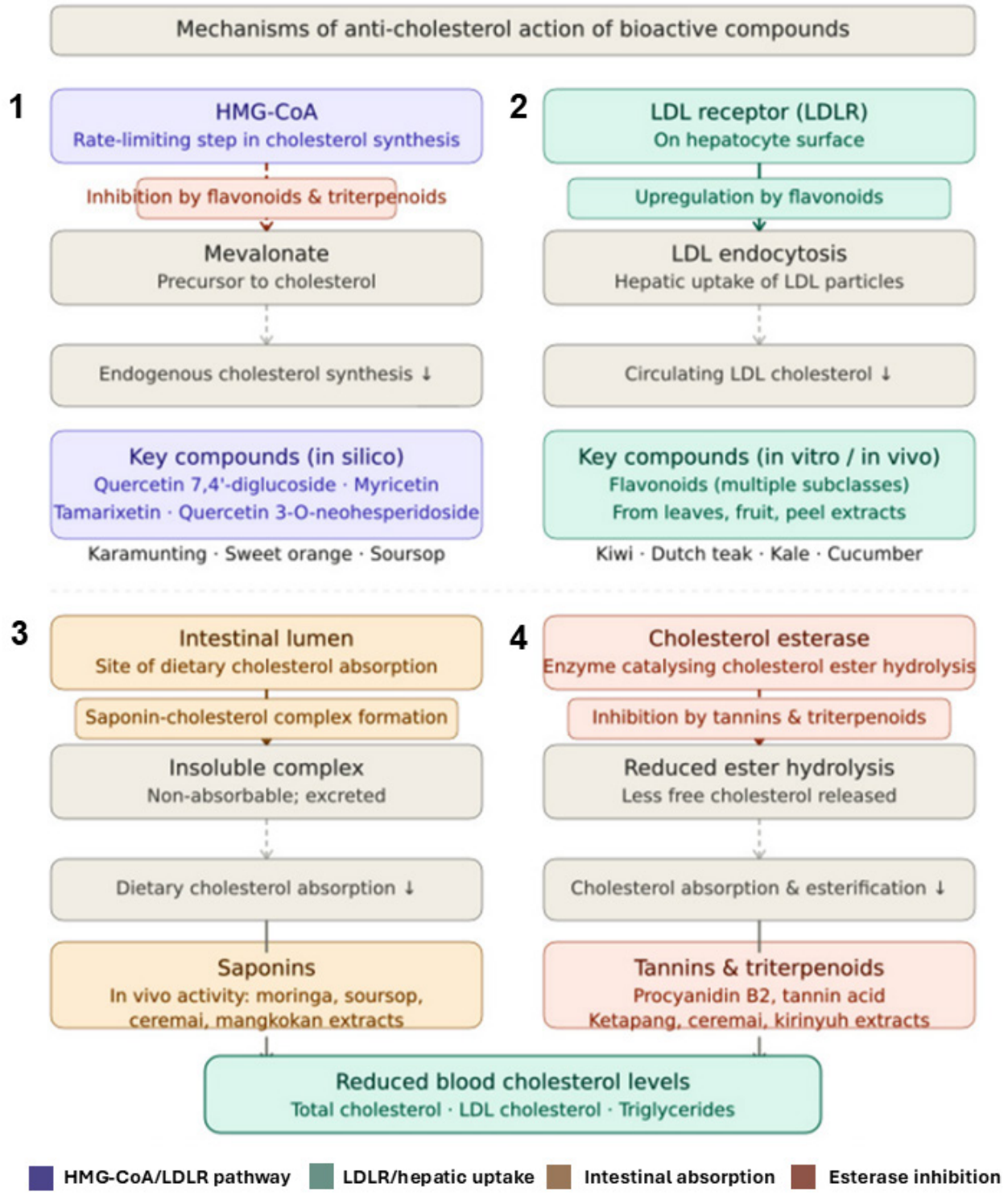

Figure 2. Proposed mechanisms of anti-cholesterol action of bioactive secondary metabolites identified from medicinal plants reviewed in this study. Four principal pathways are illustrated: (1) inhibition of HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway, primarily by quercetin-type flavonoids (quercetin 7,4'-diglucoside, myricetin, tamarixetin, quercetin 3-O-neohesperidoside) and triterpenoids, reducing endogenous cholesterol synthesis; (2) upregulation of low-density lipoprotein receptor (LDLR) expression by flavonoids, enhancing hepatic endocytosis of LDL particles and lowering circulating LDL cholesterol; (3) formation of insoluble saponin-cholesterol complexes in the intestinal lumen, reducing dietary cholesterol absorption; and (4) inhibition of cholesterol esterase by tannins and triterpenoids, reducing cholesterol ester hydrolysis and absorption. All four pathways converge on reduced blood cholesterol levels. Compounds identified through *in silico* molecular docking are indicated in pathway 1; compounds and extracts supported by *in vivo* and *in vitro* evidence are indicated in pathways 2, 3, and 4.

most favourable binding at -9.56 kcal/mol, followed by rutin (-9.22 kcal/mol), quercetin (-6.53 kcal/mol), chlorogenic acid (-5.97 kcal/mol), and catechin (-5.91 kcal/mol) [31].

In contrast, all three compounds from butterfly pea (*Clitorea ternatea* L.) — phloretin (-64.05 kcal/mol), trifolin (-59.24 kcal/mol), and trigonelline (-52.76 kcal/mol) — showed binding energies less negative than atorvastatin (-72.84 kcal/mol) [28]. Similarly, phytol from water clover (*Marsilea crenata*) yielded -6.37 kcal/mol, less negative than pravastatin (-7.13 kcal/mol) [30]. These weaker results may partly reflect differences in molecular architecture: phloretin is a dihydrochalcone, trigonelline is a pyridinium alkaloid, and phytol is a diterpene alcohol — structural classes that interact differently with the HMG-CoA reductase active site compared with the flavonoid scaffold. These compounds should be regarded as preliminary candidates requiring experimental validation.

Collectively, the *in silico* data suggest that quercetin-type flavonoids represent the most structurally consistent class of HMG-CoA reductase inhibitors across the reviewed studies. Notably, quercetin appeared as a tested compound in both karamunting (PDB 1DQ8: -9.4 kcal/mol) and soursop (PDB 1HW9: -6.53 kcal/mol), with both values more negative than their respective positive controls, suggesting consistent inhibitory potential of this scaffold across receptor conformations. However, molecular docking results must be interpreted within the limitations of computational modelling, which does not account for bioavailability, metabolism, protein binding, or pharmacokinetic behaviour [38]. Differences in docking software and PDB structures across studies also preclude direct numerical comparison of binding energies. Experimental validation through *in vitro* enzyme inhibition assays and *in vivo* models is therefore essential.

Conclusion

This review identified 14 medicinal plant species with demonstrated preclinical cholesterol-lowering activity through *in vivo* and *in vitro* studies, and five additional plants with predicted anti-cholesterol activity based on *in silico* molecular docking analyses. Plant parts utilised include leaves, bark, fruit, peel, seeds, and tubers.

In vivo studies demonstrated that extracts from kirinyuh, notika, ketapang, pumpkin, coriander, moringa, soursop, Dayak onion, mangkokan, and ceremai exhibited cholesterol-lowering activity in animal models, with most achieving efficacy comparable to simvastatin. Among these, kirinyuh (*Chromolaena odorata* L.), ceremai (*Phyllanthus acidus* (L.) Skeels), and ketapang (*Terminalia catappa* L.) are notable for achieving significant reductions at relatively low effective doses of 60, 100, and 120 mg/kg BW, respectively. *In vitro* assays demonstrated that green kiwi fruit ethanol extract possessed the greatest anti-cholesterol potency (EC50 = 7.3 ppm), followed by kale leaf (EC50 = 32.350 ppm), cucumber peel (EC50 = 122.04 ppm) and Dutch teak leaf (EC50 = 498 ppm) extracts.

In silico analyses identified quercetin-type flavonoids — including quercetin 7,4'-diglucoside and myricetin from karamunting, tamarixetin from sweet orange, and quercetin 3-O-neohesperidoside and rutin from soursop — as the most promising predicted inhibitors of HMG-CoA reductase, with binding free energies surpassing their respective statin controls. These computational findings are preliminary and require experimental validation.

Further research is required to isolate and characterise the specific active compounds responsible for the observed *in vivo* and *in vitro* activities, elucidate their mechanisms of action at the molecular level, and evaluate their safety, bioavailability, and therapeutic efficacy through well-designed clinical studies in humans.

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Conflict of interest

There is no conflict of interest in this paper. This article was written independently without affiliation with other parties.

Author contributions

MSW and NMPS conceived and designed the study. MSW collected the data. MSW and LPMKD prepared the first draft of the manuscript. MSW and NMPS analysed the data. All authors were involved in result interpretation and provided approval for the final manuscript.

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