

RESEARCH MONOGRAPH . COMPOUND PROFILE

Citrus-Bergamot

A standardized polyphenolic extract derived from Citrus bergamia Risso & Poiteau, distinguished by the presence of the 3-hydroxy-3-methylglutaryl (HMG)-conjugated flavanones brutieridin and melitidin, and investigated for cardiovascular risk factor modification through pleiotropic lipid-lowering, glycemic, hepatoprotective, and anti-inflammatory mechanisms.

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ABSTRACT

Citrus bergamot extract, derived from the juice and albedo of the bergamot orange (*Citrus bergamia* Risso & Poiteau), is a polyphenol-rich botanical preparation whose pharmacological interest centers on a distinctive flavonoid profile that includes the 3-hydroxy-3-methylglutaryl (HMG)-conjugated flavanone glycosides brutieridin and melitidin, alongside high concentrations of neoeriocitrin, naringin, and neohesperidin. These HMG-bearing flavanones are structurally analogous to the HMG-CoA substrate of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol biosynthesis and the molecular target of statin drugs. In vitro mechanistic studies in HepG2 and Caco-2 cell lines have demonstrated that bergamot polyphenolic fraction (BPF) and its principal constituents reduce HMGCR protein levels, activate AMP-activated protein kinase (AMPK) phosphorylation, stimulate fatty acid oxidation, and inhibit intestinal cholesterol absorption through downregulation of the Niemann-Pick C1-Like 1 (NPC1L1) transporter. The mechanism is therefore distinct from direct competitive HMGCR inhibition by statins and involves transcriptional and post-translational regulation of cholesterol biosynthetic and absorptive pathways.

Clinical investigation of bergamot polyphenolic extracts has been conducted primarily in Southern Italian populations with hyperlipidemia, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD). In the pivotal Mollace et al. (2011) open-label study of 237 patients with moderate hypercholesterolemia, BPF at 500 mg or 1000 mg daily for 30 days reduced total cholesterol by

22 to 31 percent, low-density lipoprotein cholesterol (LDL-C) by 24 to 36 percent, and triglycerides by 28 to 41 percent, while increasing high-density lipoprotein cholesterol (HDL-C) by 22 to 40 percent. Subsequent randomized, double-blind, placebo-controlled trials have confirmed statistically significant reductions in LDL-C and triglycerides at doses of 500 to 1300 mg daily over 6 to 24 weeks, with concurrent improvements in fasting glucose, HOMA-IR insulin resistance index, and hepatic steatosis markers. A 2020 randomized trial of a bergamot-cardoon combination (Bergacyn) in NAFLD patients over 50 years demonstrated significant reductions in liver steatosis, body weight, and hepatic transaminases.

The pharmacokinetic profile of bergamot flavonoids in humans is incompletely characterized. Oral consumption produces circulating phase II conjugated metabolites (sulfates and glucuronides of naringenin, hesperetin, and eriodictyol) detectable at 1 and 4 hours post-ingestion, consistent with intestinal deglycosylation and hepatic phase II conjugation. The characteristic HMG-conjugated flavanones brutieridin and melitidin have not been detected in plasma or urine in published pharmacokinetic studies, raising the possibility that their hypolipidemic activity is mediated locally in the gastrointestinal epithelium or through metabolites not yet characterized. The extract is generally well tolerated in clinical studies of up to 24 weeks duration, with adverse events limited to mild gastrointestinal discomfort in a minority of subjects. Bergamot contains furanocoumarins (bergamottin, bergapten) that inhibit CYP3A4, producing clinically relevant interactions with statins metabolized by this isoform (atorvastatin, simvastatin, lovastatin) and other CYP3A4 substrates. This monograph reviews the botanical identification, phytochemistry, and standardization of

bergamot extract; the molecular pharmacology of its principal flavonoid constituents; the pharmacokinetic record; the preclinical and clinical evidence base across dyslipidemia, metabolic syndrome, NAFLD, and glycemic endpoints; sourcing and quality verification; handling considerations; stack interactions; adverse-event signal; and a comparative assessment of five alternative lipid-modifying nutraceuticals (red yeast rice, berberine, plant sterols/stanols, niacin, and artichoke leaf extract) against citrus bergamot on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Botanical name: *Citrus bergamia* Risso & Poiteau (syn. *Citrus aurantium* subsp. *bergamia* (Risso & Poiteau) Wight & Arn.).

Common names: Bergamot orange, bergamot, bergamotto (Italian).

Standardized extract designations: Bergamot Polyphenolic Fraction (BPF), Bergamonte, Bergavit, Bergacyn (bergamot plus wild cardoon combination), BergaMet. These are trade or research designations for polyphenol-enriched extracts standardized to varying flavonoid content.

Family: Rutaceae, subfamily Aurantioideae, tribe Citreae.

Plant part used: Juice, albedo (white inner peel), and whole fruit of the bergamot orange. Commercial extracts are prepared primarily from the juice and albedo fractions, which contain the highest concentrations of the characteristic flavanone glycosides [1].

CAS registry numbers: No single CAS number exists for the standardized polyphenolic extract. Individual marker compounds carry the following CAS designations: naringin (10236-47-2), neoeriocitrin (13241-33-3), neohesperidin (13241-32-2). Brutieridin and melitidin do not carry widely used CAS numbers in the public domain and are identified by their spectroscopic and chromatographic characteristics.

1.2 Structural class and chemistry

Citrus bergamot extract is a multi-component botanical preparation. It is not a single molecular entity but rather a standardized mixture of polyphenolic compounds, principally flavanone and flavone glycosides. The structural class is citrus flavonoid glycoside, and the pharmacologically distinctive feature is the presence of flavanone glycosides bearing a 3-hydroxy-3-methylglutaryl (HMG) ester moiety on the sugar residue.

Principal flavanone glycosides:

Neohesperidin (eriodictyol 7-O-neohesperidoside): a flavanone disaccharide glycoside with molecular formula C₂₇H₃₂O₁₅ and molecular weight 596.53 g/mol.

Naringin (naringenin 7-O-neohesperidoside): a flavanone disaccharide glycoside with molecular formula C₂₇H₃₂O₁₄ and molecular weight 580.54 g/mol.

Neohesperidin (hesperetin 7-O-neohesperidoside): a flavanone disaccharide glycoside with molecular formula C₂₈H₃₄O₁₅ and molecular weight 610.56 g/mol.

HMG-conjugated flavanones (distinctive to bergamot):

Brutieridin: naringin esterified at the 3-hydroxyl of the rhamnose moiety with 3-hydroxy-3-methylglutaric acid. This compound is structurally analogous to HMG-CoA at the HMG moiety and is the basis for the proposed statin-like mechanism of action [2].

Melitidin: neohesperidin bearing the same HMG ester conjugation on the rhamnose sugar. Together with brutieridin, melitidin constitutes the pharmacologically distinctive pair of bergamot flavonoids not found at comparable concentrations in other citrus species [2].

Additional flavonoid constituents: Rhoifolin, chrysoeriol 7-O-neohesperidoside, diosmin, narirutin, neodiosmin, lucenin-2, vicenin-2, stellarin-2, scoparin, orientin, and apigenin 6,8-di-C-glucoside have been identified in bergamot juice and extract by liquid chromatography-mass spectrometry [3].

Furanocoumarins: Bergamottin and bergapten (5-methoxypsoralen) are present in bergamot peel oil and, at lower concentrations, in juice and albedo fractions. These compounds are responsible for the photosensitizing properties of bergamot oil and for the CYP3A4 inhibitory activity that produces drug interactions [4].

1.3 Botanical description and origin

Citrus bergamia is a small evergreen tree of the Rutaceae family, reaching 3 to 5 meters in height, with large, dark green, ovate leaves, fragrant white star-shaped flowers, and round to slightly pyriform fruits approximately 6 to 8 centimeters in diameter. The fruit is yellow-green at maturity and has a characteristically aromatic peel. The flesh is sour and not palatable as a fresh fruit, distinguishing bergamot from sweet citrus cultivars.

Genetic studies have established that bergamot orange is a hybrid, most likely between sour orange (*Citrus aurantium*) and lemon (*Citrus limon*) or between sour orange and citron (*Citrus medica*). The exact parentage remains debated, but molecular marker analysis consistently supports a bitter orange maternal lineage [5].

Commercial bergamot production is concentrated almost exclusively in the Ionian Sea coastal strip of the province of Reggio Calabria in Southern Italy. This narrow geographic region produces approximately 80 percent of the world bergamot supply and has been the source of bergamot essential oil since at least the mid-eighteenth century. Smaller plantings exist in Argentina, Brazil, Ivory Coast, and Turkey, but Calabrian bergamot is the reference standard for both essential oil and polyphenolic extract production [5].

2. Abstract

Citrus bergamot extract is a polyphenol-enriched preparation derived from the fruit of *Citrus bergamia* Risso & Poiteau, a citrus hybrid cultivated almost exclusively in the province of Reggio Calabria in Southern Italy. The extract is distinguished from other citrus polyphenol preparations by the presence of the HMG-conjugated flavanone glycosides brutieridin and melitidin, which are structurally analogous to the HMG-CoA substrate of the cholesterol biosynthetic enzyme HMGCR [2]. This structural analogy, together with the high concentrations of the flavanone glycosides neoeriocitrin, naringin, and neohesperidin, provides the mechanistic basis for the observed hypolipidemic, hypoglycemic, and hepatoprotective activities of the extract.

The principal molecular pharmacology of bergamot polyphenolic fraction (BPF) involves activation of AMP-activated protein kinase (AMPK), reduction of HMGCR protein expression, inhibition of intestinal cholesterol uptake through NPC1L1 transporter downregulation, enhancement of fatty acid beta-oxidation, and modulation of hepatic lipid metabolism [6, 7]. These mechanisms operate through transcriptional and post-translational pathways distinct from the direct competitive inhibition of HMGCR produced by statins, and the combination of cholesterol synthesis inhibition with cholesterol absorption inhibition produces a dual-mechanism lipid-lowering effect.

Clinical evidence for the hypolipidemic activity of bergamot extract has been generated in multiple trials, predominantly open-label studies and a smaller number of randomized controlled trials, enrolling patients with moderate hypercholesterolemia, mixed dyslipidemia, metabolic syndrome, type 2 diabetes mellitus, and non-alcoholic fatty liver disease. The Mollace et al. (2011) study in 237 hypercholesterolemic patients reported 22 to 31 percent reductions in total cholesterol and 24 to 36 percent reductions in LDL-C at doses of 500 to 1000 mg daily over 30 days [8]. Subsequent studies have confirmed LDL-C reductions of 15 to 36 percent, triglyceride reductions of 20 to 41 percent, and HDL-C increases of 15 to 40 percent across study populations and doses. Concurrent reductions in fasting blood glucose (15 to 25 percent), HOMA-IR insulin resistance index, and hepatic steatosis markers (AST, ALT) have been reported in metabolic syndrome and NAFLD cohorts [9, 10, 11].

The pharmacokinetic profile is incompletely characterized. Oral flavonoid bioavailability is limited by extensive intestinal and hepatic phase II metabolism (glucuronidation, sulfation), and the characteristic HMG-conjugated flavanones have not been detected as intact molecules in human plasma [12]. The extract is well tolerated in clinical studies of up to 24 weeks, with adverse events limited to mild gastrointestinal effects in a small proportion of subjects. The furanocoumarin content confers CYP3A4 inhibitory potential, producing clinically relevant interactions with CYP3A4-metabolized statins and other substrates [4].

This monograph reviews the complete pharmacological and clinical profile of citrus bergamot extract, including compound identification, phytochemistry, discovery and development history, molecular pharmacology, pharmacokinetics, pre-clinical and clinical evidence, sourcing and quality verification, handling, stack interactions, adverse-event signal, and a structured comparative assessment against five alternative lipid-modifying nutraceuticals.

3. Discovery and Development History

3.1 Traditional and historical use

The bergamot orange has been cultivated in the Calabrian coastal strip of Southern Italy since at least the fourteenth century, with the earliest documented commercial plantings dating to the sixteenth and seventeenth centuries. The primary historical application was the production of bergamot essential oil, a cold-pressed peel oil valued in perfumery, aromatherapy, and as a flavoring agent (notably in Earl Grey tea). The essential oil industry in Reggio Calabria has operated continuously since approximately 1750, and the Consorzio del Bergamotto di Reggio Calabria has served as the industry regulatory body since 1931 [5].

Traditional folk medical use of bergamot in Calabria included the consumption of bergamot juice for digestive complaints, fever reduction, and wound healing. These applications were not systematically documented in the pharmacological literature until the late twentieth century. The fruit juice and peel were also used in traditional preparations for cardiovascular health, a folk application that provided the ethnopharmacological rationale for the modern investigation of bergamot polyphenols in dyslipidemia [1].

3.2 Identification of the hypolipidemic activity

The modern pharmacological investigation of bergamot polyphenols began in the early 2000s with the work of Vincenzo Mollace and colleagues at the University of Magna Graecia in Catanzaro, Italy. The Mollace laboratory, in collaboration with Ezio Bombardelli and the Indena phytochemical group, identified the unusually high flavonoid content of bergamot juice and albedo and characterized the HMG-conjugated flavanones brutieridin and melitidin as structurally distinctive compounds with potential HMGCR-modulating activity [2].

The pivotal preclinical demonstration was reported by Miceli et al. (2007) and Leopoldini et al. (2010), who characterized the *in silico* docking of brutieridin and melitidin to the active site of HMGCR and reported *in vitro* cholesterol-lowering ac-

tivity in hepatocyte models [13, 14]. These findings established the mechanistic hypothesis that HMG-conjugated flavanones could function as natural HMGCR modulators and provided the rationale for clinical investigation.

3.3 Clinical development

The first substantial clinical study was the Mollace et al. (2011) open-label trial in 237 patients with isolated hypercholesterolemia or mixed hyperlipidemia, which reported significant reductions in total cholesterol, LDL-C, and triglycerides with increases in HDL-C at BPF doses of 500 and 1000 mg daily over 30 days [8]. This study, published in *Fitoterapia*, established the clinical evidence base and prompted the development of standardized bergamot polyphenol supplements.

Subsequent clinical development has been led primarily by Italian research groups, with contributions from Australian, Canadian, and American investigators. The Gliozzi et al. (2013) study extended the findings to patients with metabolic syndrome and NAFLD, demonstrating concurrent improvements in hepatic steatosis markers [9]. The Musolino et al. (2020) randomized controlled trial of the bergamot-cardoon combination Bergacyn in NAFLD patients confirmed hepatoprotective effects over 12 to 16 weeks [15]. The Ferro et al. (2024) randomized, double-blind, placebo-controlled trial in 80 subjects with mild to moderate hypercholesterolemia confirmed significant LDL-C reduction with a standardized bergamot extract over 12 weeks [16].

3.4 Regulatory status

Bergamot polyphenol extracts are marketed as dietary supplements in the United States, the European Union, Australia, and other jurisdictions. The extract is not approved as a pharmaceutical drug by any regulatory authority. In the European Union, bergamot extract does not carry an authorized health claim under the European Food Safety Authority (EFSA) framework. In the United States, bergamot supplements are marketed under the Dietary Supplement Health and Education Act (DSHEA) of 1994 and may not bear disease claims. The Botanical Safety Handbook classifies bergamot as Class 1 (safest category) with Class A interaction potential (lowest herb-drug interaction risk), though this classification was established for the whole fruit and essential oil rather than for the concentrated polyphenolic extract [17].

4. Mechanism of Action

Bergamot polyphenolic fraction exerts its pharmacological effects through multiple molecular targets operating in the cholesterol biosynthetic pathway, the cholesterol absorption pathway, and the cellular energy-sensing and lipid metabolism pathways. The mechanism is pleiotropic and involves at least four characterized molecular activities.

4.1 HMGCR modulation

The structural analogy between the HMG moiety of brutieridin and melitidin and the HMG-CoA substrate of HMGCR provided the original mechanistic hypothesis for bergamot hypolipidemic activity. In silico molecular docking studies have demonstrated that brutieridin and melitidin can occupy the active site of HMGCR in a conformation overlapping with the statin binding site [13, 14].

However, direct enzymatic inhibition studies have produced a more nuanced picture. The Ballistreri et al. (2021) investigation in HepG2 cells demonstrated that bergamot fruit extract and its individual constituents do not directly inhibit HMGCR catalytic activity in cell-free enzyme assays, but that bergamot fruit extract and neohesperidin decrease HMGCR protein levels in intact hepatocytes [6]. The mechanism is therefore post-translational rather than competitive: bergamot polyphenols promote HMGCR protein degradation through the ubiquitin-proteasome pathway rather than occupying the catalytic site as competitive inhibitors. This distinction is pharmacologically important because it implies a different dose-response relationship and a different potential for combination with statins than would be expected from a simple competitive HMGCR inhibitor.

4.2 AMPK activation

AMP-activated protein kinase (AMPK) is a central energy-sensing kinase that, when phosphorylated and activated, promotes catabolic pathways (fatty acid oxidation, glucose uptake) and suppresses anabolic pathways (lipogenesis, cholesterol synthe-

sis). Bergamot polyphenolic fraction and the individual constituent neohesperidin have been shown to increase AMPK phosphorylation at Thr172 in HepG2 hepatocytes [6, 7].

AMPK activation produces downstream phosphorylation and inactivation of acetyl-CoA carboxylase (ACC), the rate-limiting enzyme in fatty acid synthesis, and promotes fatty acid beta-oxidation. AMPK also phosphorylates HMGCR at Ser872, producing allosteric inactivation of the enzyme. The AMPK pathway therefore provides a second, indirect mechanism for HMGCR suppression that is mechanistically complementary to the post-translational protein degradation pathway [7].

The AMPK activation by bergamot polyphenols is also the principal molecular basis for the observed effects on glucose metabolism. AMPK activation in skeletal muscle and adipose tissue promotes GLUT-4 translocation and glucose uptake, and in hepatocytes it suppresses gluconeogenic gene expression. These effects provide the mechanistic substrate for the reductions in fasting glucose and HOMA-IR reported in clinical studies [10].

4.3 Cholesterol absorption inhibition

Brutieridin, a principal HMG-conjugated flavanone of bergamot, has been demonstrated to reduce cholesterol uptake in Caco-2 intestinal epithelial cells through downregulation of Niemann-Pick C1-Like 1 (NPC1L1), the key cholesterol transporter mediating intestinal cholesterol absorption [6]. NPC1L1 is the molecular target of ezetimibe, the clinically used cholesterol absorption inhibitor. The brutieridin-mediated NPC1L1 downregulation therefore adds a cholesterol absorption inhibition mechanism to the cholesterol synthesis inhibition mechanisms described above, producing a dual-pathway hypolipidemic effect.

4.4 Anti-inflammatory and antioxidant activity

Bergamot polyphenols, particularly naringin, neoeriocitrin, and neohesperidin, possess documented anti-inflammatory and antioxidant activities. Naringenin (the aglycone of naringin released by intestinal deglycosylation) inhibits NF-kappaB signaling, reduces pro-inflammatory cytokine production (TNF-alpha, IL-1 beta, IL-6), and scavenges reactive oxygen species [18]. These anti-inflammatory mechanisms

contribute to the vascular protective effects observed in clinical studies and to the hepatoprotective activity in NAFLD, where oxidative stress and inflammatory signaling are central pathogenic mechanisms.

4.5 Insulin-sensitizing mechanisms

Naringenin has been demonstrated to enhance sirtuin-1 (SIRT1) activity, promoting deacetylation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha) and increasing mitochondrial biogenesis and fatty acid oxidation [10]. In adipocytes and skeletal muscle cells, naringenin promotes GLUT-4 translocation to the cell surface through AMPK-dependent and AMPK-independent pathways, increasing insulin-stimulated glucose uptake. These molecular activities provide the mechanistic basis for the improvements in insulin sensitivity and glycemic control reported in metabolic syndrome populations.

4.6 Composite pharmacology

The composite pharmacology of bergamot polyphenolic fraction therefore involves at least four convergent mechanisms: (1) reduction of HMGCR protein levels through post-translational degradation; (2) AMPK-mediated phosphorylation and inactivation of HMGCR and ACC, suppressing cholesterol and fatty acid synthesis while promoting beta-oxidation; (3) NPC1L1 downregulation reducing intestinal cholesterol absorption; and (4) anti-inflammatory and antioxidant activity reducing vascular and hepatic inflammatory signaling. The convergence of these mechanisms on the lipid metabolic pathway distinguishes bergamot extract from single-target interventions and provides a pharmacological rationale for the magnitude of the lipid-lowering effects observed in clinical studies.

5. Pharmacokinetics

5.1 Absorption and bioavailability

The oral bioavailability of bergamot flavonoid glycosides follows the general pattern established for citrus flavanones: the glycosidic forms (naringin, neoeriodictin, neohesperidin) are poorly absorbed intact and require hydrolysis of the sugar moiety by intestinal beta-glucosidases and colonic microbiota to release the bioactive aglycones (naringenin, eriodictyol, hesperetin) [12].

The Ferrara et al. (2018) pharmacokinetic study in healthy human volunteers consuming bergamot juice detected up to 12 flavanone phase II conjugates (sulfates and glucuronides of naringenin, hesperetin, and eriodictyol) in plasma at 1 and 4 hours post-consumption [12]. Maximum plasma concentrations of individual conjugated metabolites were in the low nanomolar to low micromolar range. The time to peak plasma concentration was approximately 4 hours for the principal metabolites, consistent with intestinal transit, microbiota-mediated deglycosylation, absorption of aglycones from the distal small intestine and colon, and hepatic phase II conjugation.

Notably, the HMG-conjugated flavanones brutieridin and melitidin, which are the pharmacologically distinctive compounds of bergamot, were not detected as intact molecules in plasma or urine in the Ferrara et al. study despite targeted analytical methods [12]. This observation has several possible interpretations: (1) brutieridin and melitidin may be completely hydrolyzed in the intestinal lumen, releasing the flavanone glycoside and free HMG acid before absorption; (2) the intact molecules may be absorbed at concentrations below the analytical detection limit; or (3) the hypolipidemic activity of these compounds may be exerted locally in the intestinal epithelium (consistent with the NPC1L1 downregulation mechanism) rather than through systemic exposure.

5.2 Distribution

No formal distribution studies (volume of distribution, tissue partitioning) have been conducted with bergamot polyphenolic extract in humans. By analogy with other citrus flavanones, the absorbed phase II metabolites are expected to circulate

predominantly bound to plasma proteins (albumin, approximately 60 to 80 percent binding for naringenin) and to distribute to tissues with moderate volume of distribution [19].

5.3 Metabolism

Bergamot flavanones undergo extensive first-pass metabolism. The primary metabolic pathways are: (1) intestinal deglycosylation by beta-glucosidases and lactase-phlorizin hydrolase, releasing flavanone aglycones; (2) colonic microbiota-mediated ring cleavage and dehydroxylation producing phenylpropionic acid and phenylacetic acid metabolites; and (3) hepatic phase II conjugation (glucuronidation by UDP-glucuronosyltransferases, sulfation by sulfotransferases) of absorbed aglycones [12, 19].

The furanocoumarin bergamottin undergoes CYP3A4-mediated oxidation and forms a reactive intermediate that irreversibly inactivates CYP3A4 through mechanism-based inhibition. This suicide inhibition is the molecular basis for the drug interaction potential of bergamot with CYP3A4 substrates [4].

5.4 Elimination

Elimination of bergamot flavanone metabolites occurs through renal excretion of phase II conjugates and through biliary excretion of glucuronide conjugates, with enterohepatic recirculation contributing to a secondary plasma concentration peak observed with some citrus flavanones at 8 to 12 hours post-ingestion [19]. The terminal elimination half-life of naringenin phase II metabolites is approximately 2 to 4 hours based on studies with grapefruit juice naringenin pharmacokinetics.

5.5 Routes of administration

Oral administration is the sole route used clinically and in research. Bergamot polyphenolic extract is supplied as capsules or tablets containing 150 to 1000 mg of standardized extract per unit. Juice consumption is an alternative but delivers a lower and more variable polyphenol dose than standardized extract.

5.6 Special populations

No formal pharmacokinetic studies in renal impairment, hepatic impairment, pediatric, or geriatric populations have been conducted with bergamot polyphenolic extract. Given the hepatic metabolism of the flavanone constituents, hepatic impairment may alter exposure to active metabolites. The extract has not been studied in pregnant or lactating women, and use in these populations is not recommended owing to insufficient safety data.

6. Preclinical Pharmacology

6.1 In vitro studies

The Ballistreri et al. (2021) investigation in HepG2 hepatocytes and Caco-2 intestinal epithelial cells is the most comprehensive mechanistic study of bergamot extract in cell culture [6]. Principal findings include: bergamot fruit extract (50 to 200 micrograms per milliliter) reduced intracellular cholesterol content in HepG2 cells by 20 to 40 percent; neohesperidin was the most potent individual constituent for HMGCR protein reduction; brutieridin produced the greatest reduction in NPC1L1-mediated cholesterol uptake in Caco-2 cells; and AMPK phosphorylation was increased by both the whole extract and neohesperidin at concentrations of 50 to 100 micrograms per milliliter.

Additional in vitro studies have demonstrated: anti-inflammatory activity of bergamot polyphenols in lipopolysaccharide-stimulated macrophages (reduction of TNF-alpha and IL-6 secretion) [18]; antioxidant activity in DPPH, ABTS, and ORAC radical scavenging assays; and anti-proliferative activity in several cancer cell lines, though the latter observation has not been advanced to in vivo models of clinical relevance [3].

6.2 Animal models

The Parafati et al. (2015) study demonstrated that BPF administration to cafeteria-diet-fed rats (a model of metabolic syndrome) prevented the development of non-alcoholic fatty liver disease through stimulation of lipophagy (selective autophagy of lipid droplets) [20]. BPF treatment reduced hepatic triglyceride accumulation, decreased liver weight, and normalized hepatic histology. The mechanism was attributed to AMPK activation and downstream induction of autophagy pathways.

The La Russa et al. (2020) study in high-fat-diet-fed mice confirmed that bergamot polyphenols improved dyslipidemia, reduced hepatic lipid accumulation, and attenuated pathophysiological features of NAFLD including lobular inflammation, hepatocyte ballooning, and fibrotic markers [21]. These findings were replicated in

a rat model of hyperlipidemia, where BPF reduced total cholesterol and LDL-C while modulating PCSK9 expression through an antioxidant-dependent pathway [22].

The Musolino et al. (2019) study in a Bergacyn-treated animal model demonstrated synergistic effects of bergamot polyphenols and wild cardoon (*Cynara cardunculus*) extract on hepatic lipid metabolism, with the combination producing greater reductions in hepatic triglyceride content and transaminase levels than either component alone [15].

6.3 Pharmacodynamic summary

The preclinical pharmacology of bergamot polyphenolic extract supports a multi-target mechanism of lipid lowering and metabolic improvement that includes: hepatic HMGCR protein reduction (not direct catalytic inhibition); AMPK activation with downstream ACC inactivation and enhanced fatty acid oxidation; intestinal NPC1L1-mediated cholesterol absorption inhibition; stimulation of hepatic lipophagy; anti-inflammatory cytokine suppression; and antioxidant radical scavenging. The magnitude of the lipid-lowering effect in animal models (20 to 40 percent LDL-C reduction) is broadly consistent with the clinical effect sizes observed in human studies.

7. Clinical Evidence Base

7.1 Dyslipidemia

The Mollace et al. (2011) study is the largest and most frequently cited clinical investigation of bergamot polyphenolic extract in dyslipidemia [8]. In an open-label design, 237 patients with isolated hypercholesterolemia (n=104) or mixed hyperlipidemia (n=133) received BPF at 500 mg daily, 1000 mg daily, or placebo for 30 days. In the hypercholesterolemia subgroup, BPF 1000 mg daily produced reductions of 30.8 percent in total cholesterol, 36.0 percent in LDL-C, and 28.1 percent in triglycerides, with a 40.1 percent increase in HDL-C. In the mixed hyperlipidemia subgroup, BPF 1000 mg daily produced reductions of 22.3 percent in total cholesterol, 24.1 percent in LDL-C, and 41.1 percent in triglycerides, with a 22.0 percent increase in HDL-C. The 500 mg dose produced intermediate effects. No placebo response was observed.

The Ferro et al. (2024) randomized, double-blind, placebo-controlled trial enrolled 80 subjects with mild to moderate hypercholesterolemia and randomized them to bergamot extract 500 mg daily or placebo for 12 weeks [16]. The bergamot group showed statistically significant reductions in total cholesterol (approximately 15 percent) and LDL-C (approximately 18 percent) compared to placebo, with no significant differences in adverse-event rates.

The Toth et al. (2016) prospective study followed patients with moderate hypercholesterolemia receiving BPF 1000 mg daily for 6 months and demonstrated sustained reductions in LDL-C, reductions in atherogenic small dense LDL particles, and reductions in subclinical atherosclerosis markers (carotid intima-media thickness) [23].

A subgroup analysis in patients concurrently receiving statin therapy (rosuvastatin 10 mg or 20 mg daily) demonstrated that the addition of BPF 1000 mg daily produced incremental LDL-C reduction beyond the statin effect, with the combination of rosuvastatin 10 mg plus BPF producing LDL-C reductions comparable to rosuvastatin 20 mg alone, suggesting potential for statin dose reduction strategies [8].

7.2 Metabolic syndrome

The Gliozzi et al. (2013) study evaluated BPF in patients with metabolic syndrome (defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria) [9]. BPF at 650 mg twice daily (1300 mg daily) for 120 days produced significant reductions in total cholesterol, LDL-C, triglycerides, and fasting blood glucose, with increases in HDL-C and significant improvements in HOMA-IR insulin resistance index. Concurrent reduction in hepatic steatosis was documented by ultrasonographic assessment.

The Capomolla et al. (2019) study of a pectin-enriched formulation of bergamot polyphenols in metabolic syndrome patients demonstrated reductions in the atherogenic index of plasma and reductions in body weight over 6 months of treatment [24]. The weight reduction (approximately 3 to 5 percent of baseline body weight) was modest but statistically significant and was attributed to the AMPK-mediated increase in fatty acid oxidation and the modest appetite-suppressing effect of pectin.

7.3 Non-alcoholic fatty liver disease

The Gliozzi et al. (2013) study included a NAFLD subgroup analysis in which BPF treatment was associated with significant reductions in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), with ultrasonographic evidence of reduced hepatic steatosis [9]. The Parafati et al. (2015) preclinical demonstration of lipophagy stimulation provided the mechanistic basis for these clinical observations [20].

The Musolino et al. (2020) randomized clinical trial evaluated Bergacyn (a combination of bergamot polyphenol extract and wild cardoon extract) in non-diabetic individuals over 50 years with documented hepatic steatosis [15]. Subjects were randomized to placebo, bergamot extract alone, wild cardoon extract alone, or the Bergacyn combination for 12 weeks. The Bergacyn group showed statistically significant reductions in liver steatosis grade (by ultrasonographic assessment), body weight, and serum transaminases compared to placebo. The combination was more effective than either component alone, supporting a synergistic interaction. AST decreased by approximately 15 points and ALT by approximately 18 points in the combination group, compared to approximately 10-point reductions with the individual extracts.

7.4 Glycemic endpoints

Multiple studies have reported reductions in fasting blood glucose in patients receiving bergamot polyphenolic extract, with reductions ranging from 15 to 25 percent depending on baseline glucose level, dose, and duration [8, 9, 10]. The Mollace et al. (2011) study reported fasting glucose reductions of approximately 18 to 22 percent in the mixed hyperlipidemia subgroup [8]. The Gliozzi et al. (2013) metabolic syndrome study reported significant glucose reduction with concurrent improvement in HOMA-IR [9].

A three-arm, placebo-controlled, double-blind clinical trial of a standardized bergamot phytoextract reported that the 1300 mg daily dose produced an 18.1 percent reduction in fasting blood sugar after 90 days, with a 12.2 percent reduction in HOMA-IR [10].

However, conflicting evidence exists. A randomized, double-blind, placebo-controlled study of a combination formulation containing bergamot, fenugreek, and olive leaf extract in patients with prediabetes failed to demonstrate significant changes in glycemic profile after 6 months of treatment [25]. This null result may reflect the specific formulation, the dose of bergamot within the combination, or the population studied, but it tempers the glycemic claims and underscores the need for adequately powered, bergamot-specific glycemic trials.

7.5 Antipsychotic-associated metabolic dysfunction

A 60-day open-label study evaluated low-dose BPF (500 mg daily) in patients receiving second-generation antipsychotic medications with metabolic side effects [26]. The study did not demonstrate significant improvements in metabolic parameters at this dose. The authors concluded that higher BPF doses may be required to overcome the metabolic perturbations induced by antipsychotic therapy and that the negative result should not be extrapolated to higher-dose regimens or to populations without antipsychotic-induced metabolic dysfunction.

7.6 Vascular reactivity

The Mollace et al. (2011) study reported improvements in endothelium-dependent flow-mediated dilation in patients receiving BPF, consistent with the anti-inflammatory and antioxidant mechanisms [8]. The Toth et al. (2016) prospective study reported reductions in carotid intima-media thickness after 6 months of BPF supple-

mentation, suggesting an anti-atherogenic effect beyond lipid lowering [23]. These vascular endpoints are hypothesis-generating but have not been replicated in adequately powered randomized controlled trials with hard cardiovascular outcomes.

8. Sourcing and Quality Verification

8.1 Extract standardization

Bergamot polyphenolic extract quality is defined by the total polyphenol content and by the concentrations of the five principal flavanone glycosides (neoeriocitrin, naringin, neohesperidin, brutieridin, melitidin). Standardized commercial extracts typically specify total polyphenol content by the Folin-Ciocalteu assay (commonly 25 to 38 percent w/w) and identify brutieridin and melitidin as marker compounds by high-performance liquid chromatography (HPLC) [1].

The BPF preparation used in the Mollace et al. (2011) and subsequent Italian clinical trials was standardized to approximately 38 percent total flavonoid content by weight and was prepared by aqueous extraction of bergamot juice and albedo followed by adsorption chromatography and spray-drying [8]. The BergaMet commercial preparation, marketed principally in Australia, North America, and Europe, is standardized to 38 to 47 percent polyphenol content.

8.2 Source material

Calabrian bergamot (from the Reggio Calabria province) is the reference source material for polyphenolic extract production. The flavonoid profile, particularly the brutieridin and melitidin content, varies with cultivar, harvest date, fruit maturity, and extraction method [3]. Early-harvest fruit (green stage) contains higher concentrations of certain flavonoids than fully mature fruit, and some commercial preparations specify harvest timing as a quality parameter.

8.3 Quality verification

Investigators should confirm extract identity and quality through:

- HPLC quantification of neoeriocitrin, naringin, neohesperidin, brutieridin, and melitidin against reference standards
- Total polyphenol content by Folin-Ciocalteu or equivalent colorimetric assay

- Heavy metal analysis (lead, cadmium, arsenic, mercury) per USP or equivalent standards
- Pesticide residue analysis appropriate for citrus fruits grown in Mediterranean agricultural conditions
- Furanocoumarin content assessment (bergamottin, bergapten), particularly for preparations derived from peel-inclusive processing, to characterize the CYP3A4 interaction potential
- Microbial testing (total plate count, yeast and mold, absence of Salmonella, E. coli, and Staphylococcus aureus)

Lot-to-lot variability is a recognized concern with botanical extracts. Third-party analytical confirmation of manufacturer certificates of analysis is appropriate for any investigation where dose-response precision is important. The natural-product character of the extract introduces inherent variability that does not apply to single-entity pharmaceutical compounds and should be factored into study design and interpretation.

9. Reconstitution and Handling

Bergamot polyphenolic extract is supplied as a dry powder (spray-dried from aqueous extract) in capsule, tablet, or bulk powder form. The powder is hygroscopic and should be stored in airtight containers protected from moisture.

Storage conditions: Room temperature (15 to 25 degrees Celsius) in a cool, dry location. Refrigerated storage (2 to 8 degrees Celsius) extends stability but is not required for short-term storage of the dry powder. Avoid prolonged exposure to temperatures above 30 degrees Celsius, direct sunlight, and high humidity (greater than 60 percent relative humidity).

Stability: The flavonoid glycosides in bergamot extract are generally stable in the dry state under recommended storage conditions for at least 24 months. Accelerated stability testing (40 degrees Celsius, 75 percent relative humidity) has demonstrated acceptable stability for 6 months in properly packaged capsule formulations.

Solution preparation for in vitro work: For cell culture studies, bergamot extract is typically dissolved in dimethyl sulfoxide (DMSO) at stock concentrations of 50 to 100 mg/mL, with working dilutions prepared in cell culture medium. Final DMSO concentration should not exceed 0.1 percent v/v. Alternatively, aqueous stock solutions can be prepared at lower concentrations (1 to 10 mg/mL) for water-soluble preparations, with dissolution assisted by brief sonication.

Aliquoting: Stock solutions should be aliquoted for single-use to avoid repeated freeze-thaw cycles. Polyphenol solutions are susceptible to oxidative degradation; preparation under nitrogen atmosphere and storage at minus 20 degrees Celsius in amber glass or polypropylene tubes is recommended for in vitro research applications.

Light sensitivity: Citrus flavonoids undergo slow photodegradation. Light protection (amber containers, foil wrapping) is recommended for both dry powder and solution storage, particularly for analytical reference solutions.

10. Stack Interactions and Combinations

Bergamot polyphenolic extract interacts with several drug classes through its furanocoumarin-mediated CYP3A4 inhibition and through its pharmacodynamic lipid-lowering and glycemic effects. Investigators and practitioners should consider the following interactions.

CYP3A4-metabolized statins: Bergamot contains bergamottin and related furanocoumarins that irreversibly inhibit CYP3A4 through mechanism-based inactivation [4]. Statins metabolized by CYP3A4 (atorvastatin, simvastatin, lovastatin) may have elevated plasma concentrations when co-administered with bergamot extract, increasing the risk of myopathy and rhabdomyolysis. This interaction is analogous to the well-characterized grapefruit-statin interaction. Pravastatin and rosuvastatin, which are not CYP3A4 substrates, are not expected to be affected. Investigators combining bergamot with CYP3A4-metabolized statins should consider statin dose reduction and monitoring for myopathy symptoms (muscle pain, weakness, dark urine, elevated creatine kinase).

Other CYP3A4 substrates: Benzodiazepines (midazolam, triazolam, alprazolam), calcium channel blockers (felodipine, nifedipine, verapamil), immunosuppressants (cyclosporine, tacrolimus), and certain antiretroviral agents are CYP3A4 substrates that may be affected by bergamot furanocoumarin content. The clinical relevance depends on the furanocoumarin content of the specific extract preparation, which varies with extraction method and peel inclusion.

Antidiabetic medications: Bergamot polyphenols reduce fasting blood glucose through AMPK activation and insulin sensitization [10]. Concurrent use with metformin (also an AMPK activator), sulfonylureas, insulin, or SGLT2 inhibitors may produce additive hypoglycemic effects. Blood glucose monitoring is recommended when initiating bergamot supplementation in patients on antidiabetic therapy.

Anticoagulant and antiplatelet agents: Citrus flavonoids have demonstrated modest antiplatelet activity in vitro. The clinical significance of this interaction is not established, but caution is warranted in patients on warfarin, direct oral antico-

agulants, or antiplatelet agents (aspirin, clopidogrel). INR monitoring is reasonable when initiating bergamot supplementation in warfarin-treated patients.

Other lipid-lowering nutraceuticals: Combination with red yeast rice (which contains monacolin K, a naturally occurring lovastatin analog metabolized by CYP3A4) presents a dual interaction concern: pharmacodynamic additivity on lipid lowering plus pharmacokinetic CYP3A4 inhibition increasing monacolin K exposure. This combination should be approached with caution. Combination with berberine is pharmacodynamically additive on AMPK activation and lipid lowering; no characterized pharmacokinetic interaction exists, and the combination has been used in clinical studies with acceptable tolerability [27]. Combination with plant sterols/stanols is pharmacodynamically complementary (cholesterol absorption inhibition by plant sterols plus synthesis inhibition and AMPK activation by bergamot) and is not expected to produce pharmacokinetic interaction.

Ezetimibe: Bergamot and ezetimibe share the NPC1L1 transporter as a molecular target for cholesterol absorption inhibition. Concurrent use may produce pharmacodynamic redundancy at this target, with uncertain clinical benefit beyond either agent alone.

11. Adverse Events and Safety

11.1 Common adverse events

Bergamot polyphenolic extract is well tolerated in clinical studies of up to 24 weeks duration. The principal adverse events reported across studies are:

- Mild gastrointestinal discomfort (nausea, epigastric fullness, heartburn): reported in approximately 3 to 8 percent of subjects in clinical trials, generally mild and self-limiting [8, 16]
- Headache: reported in approximately 2 to 5 percent of subjects, comparable to placebo rates in controlled trials
- Allergic reactions (skin rash, pruritus): rare, reported in individuals with known citrus hypersensitivity

The adverse-event profile in clinical trials has been consistently favorable, with no statistically significant differences between bergamot and placebo groups in the randomized controlled trials that have been completed [16].

11.2 Photosensitivity

Bergamot essential oil and, to a lesser extent, juice and albedo fractions contain the furanocoumarins bergapten (5-methoxypsoralen) and bergamottin, which produce phototoxic dermatitis (berloque dermatitis) on topical application followed by ultraviolet light exposure [4]. This photosensitivity concern applies primarily to topical bergamot oil rather than to orally administered polyphenolic extract, but the furanocoumarin content of specific extract preparations should be assessed. Most modern bergamot supplement formulations are derived from juice and albedo fractions with lower furanocoumarin content than the peel oil, and some preparations specify furanocoumarin-free or low-furanocoumarin status.

11.3 Drug interaction safety concerns

The CYP3A4 inhibition by bergamot furanocoumarins represents the most clinically significant safety concern. The interaction with CYP3A4-metabolized statins (atorvastatin, simvastatin, lovastatin) can elevate statin plasma concentrations to the range associated with myopathy and rhabdomyolysis risk. This interaction has been well characterized for grapefruit (which contains the same furanocoumarins) and is expected to apply to bergamot preparations containing meaningful furanocoumarin concentrations [4]. The magnitude of the interaction depends on the furanocoumarin content of the specific preparation, the dose of bergamot, and the dose of the co-administered statin.

11.4 Long-term safety

Long-term safety data (greater than 6 months) for bergamot polyphenolic extract are limited. The 6-month Toth et al. (2016) prospective study reported no safety signals beyond those observed in shorter-term studies [23]. However, the absence of large, long-duration safety studies limits the confidence with which long-term safety can be characterized. The flavonoid class generally has a favorable long-term safety profile based on dietary intake data, but the concentrated polyphenolic extract delivers flavonoid doses substantially above typical dietary intake, and extrapolation from dietary safety data should be made cautiously.

11.5 Pregnancy and lactation

No human pregnancy or lactation safety data exist for bergamot polyphenolic extract. Use in pregnancy and lactation is not recommended.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative lipid-modifying nutraceuticals against citrus bergamot extract, evaluated against five competency standards: novelty of mechanism, effect size on lipid endpoints, current clinical trajectory and regulatory status, side-effect profile, and overall validation (quality and depth of clinical evidence). The five comparators were selected as the principal non-pharmaceutical lipid-modifying interventions with substantive clinical evidence.

12.1 Red Yeast Rice (*Monascus purpureus* extract)

Mechanism: Red yeast rice contains monacolin K (chemically identical to lovastatin), a competitive HMGCR inhibitor. The mechanism is direct statin-equivalent competitive inhibition of the HMGCR catalytic site, fundamentally different from the AMPK-mediated and post-translational HMGCR modulation produced by bergamot polyphenols [28].

Effect size: Meta-analyses of randomized controlled trials demonstrate LDL-C reductions of 15 to 25 percent with standardized red yeast rice preparations delivering 3 to 10 mg of monacolin K daily. A large Chinese randomized controlled trial (CCSPS, n=4870) demonstrated a 45 percent reduction in coronary events with Xuezhikang red yeast rice preparation over 4.5 years, the only nutraceutical with a positive hard cardiovascular outcome trial [28].

Novelty: Low. The mechanism is identical to statin therapy. Monacolin K is lovastatin.

Current trajectory: Regulatory position is complex. The European Food Safety Authority has issued a safety opinion raising concerns about monacolin K in food supplements at doses above 3 mg daily. Several EU member states have restricted or banned red yeast rice supplements containing significant monacolin K. In the United States, the FDA has taken enforcement action against red yeast rice products containing quantifiable lovastatin as unapproved new drugs. The regulatory trajectory is restrictive.

Side-effect profile: Adverse events mirror statin therapy at the corresponding monacolin K dose: myalgia (3 to 7 percent), hepatic transaminase elevation (rare), gastrointestinal discomfort. The compound depletes coenzyme Q10 through HMGCR inhibition, as do pharmaceutical statins. Contamination with citrinin (a nephrotoxic mycotoxin produced by *Monascus* species) has been documented in some commercial preparations and is a quality concern unique to this compound [28].

Overall validation: High. The evidence base includes a positive cardiovascular outcomes trial, multiple meta-analyses, and regulatory-authority scientific opinions. The validation level exceeds that of any other lipid-modifying nutraceutical, including bergamot.

Comparison to bergamot: Red yeast rice has substantially stronger clinical evidence, including a cardiovascular outcomes trial that bergamot lacks. Bergamot has a differentiated mechanism (AMPK activation, NPC1L1 modulation) rather than direct HMGCR competitive inhibition, does not share the statin-associated coenzyme Q10 depletion or myalgia signal, and offers additional glycemic and hepato-protective effects that red yeast rice does not. Bergamot also has a more favorable regulatory trajectory. The two compounds are mechanistically complementary but the combination raises the CYP3A4 interaction concern (bergamot furanocoumarins inhibiting monacolin K metabolism).

12.2 Berberine

Mechanism: Berberine activates AMPK, upregulates LDL receptor expression through a post-transcriptional mechanism (stabilization of LDL receptor mRNA), and inhibits PCSK9 expression. The AMPK activation mechanism is shared with bergamot polyphenols; the LDL receptor and PCSK9 mechanisms are distinct [27].

Effect size: Meta-analyses report LDL-C reductions of 20 to 25 percent, triglyceride reductions of 20 to 30 percent, and modest HDL-C increases with berberine 500 to 1500 mg daily. These effect sizes are broadly comparable to bergamot polyphenolic extract [27].

Novelty: Moderate. The AMPK activation mechanism is shared with bergamot, but the LDL receptor upregulation through mRNA stabilization and the PCSK9 inhibition are mechanistically distinct and pharmacologically interesting.

Current trajectory: Active. Multiple clinical trials ongoing. Berberine is extensively available as a dietary supplement globally. The compound is a traditional Chinese medicine component with centuries of use for gastrointestinal infections. No regulatory restrictions on supplement sales in major markets.

Side-effect profile: Gastrointestinal adverse events (diarrhea, constipation, nausea, abdominal pain) are the principal concern, reported in 10 to 30 percent of subjects at doses above 1000 mg daily. The gastrointestinal signal is more pronounced than that of bergamot. Berberine also has CYP3A4, CYP2D6, and P-glycoprotein inhibitory activity, producing multiple drug interactions [27].

Overall validation: Moderate to high. Extensive clinical trial literature, multiple meta-analyses, strong mechanistic characterization. No cardiovascular outcomes trial.

Comparison to bergamot: Berberine and bergamot share AMPK activation as a mechanism but differ in additional pathways (LDL receptor and PCSK9 for berberine; NPC1L1 and anti-inflammatory for bergamot). Effect sizes on LDL-C are comparable. Bergamot has a more favorable gastrointestinal tolerability profile. The combination has been studied clinically with acceptable tolerability and additive lipid-lowering effects [27].

12.3 Plant Sterols and Stanols

Mechanism: Plant sterols (beta-sitosterol, campesterol, stigmasterol) and stanols (sitostanol, campestanol) inhibit intestinal cholesterol absorption by competing with cholesterol for incorporation into mixed micelles and for NPC1L1-mediated uptake. The mechanism is purely absorptive, with no effect on cholesterol synthesis or hepatic lipid metabolism [29].

Effect size: Meta-analyses demonstrate LDL-C reductions of 8 to 12 percent at the recommended intake of 2 grams daily. No significant effects on triglycerides or HDL-C. The effect size is smaller than that reported for bergamot polyphenolic extract, red yeast rice, or berberine [29].

Novelty: Low. The mechanism has been characterized for over 50 years and is well established in clinical nutrition.

Current trajectory: Stable. Plant sterols and stanols carry authorized health claims in the EU (EFSA-approved) and in the United States (FDA-qualified). They are incorporated into functional foods (margarines, yogurt drinks) with wide market availability.

Side-effect profile: Very favorable. No significant adverse events at recommended doses. Concerns about potential interference with fat-soluble vitamin absorption (beta-carotene, vitamin E) at high doses have been raised but not consistently demonstrated. Rare genetic condition phytosterolemia contraindicates use [29].

Overall validation: High. Extensive clinical evidence, regulatory-authority-approved health claims, meta-analyses. No cardiovascular outcomes trial as monotherapy.

Comparison to bergamot: Plant sterols have stronger regulatory validation (authorized health claims) and a longer safety track record, but substantially smaller LDL-C effect sizes (8 to 12 percent versus 18 to 36 percent for bergamot). Plant sterols lack the glycemic, hepatoprotective, and anti-inflammatory effects of bergamot. The two compounds are mechanistically complementary (plant sterols for cholesterol absorption, bergamot for synthesis inhibition and AMPK activation) and the combination is pharmacologically rational.

12.4 Niacin (Nicotinic Acid)

Mechanism: Niacin inhibits hepatic diacylglycerol acyltransferase 2, reducing triglyceride synthesis and VLDL secretion; activates the GPR109A receptor; and increases HDL-C through reduced hepatic HDL catabolism. The mechanism is entirely distinct from bergamot polyphenol pharmacology [30].

Effect size: Niacin produces the largest HDL-C increases of any lipid-modifying agent (15 to 35 percent at 1 to 3 grams daily), with LDL-C reductions of 10 to 20 percent and triglyceride reductions of 20 to 40 percent. The HDL-C effect exceeds that of bergamot, but the cardiovascular benefit of niacin-mediated HDL-C elevation has been questioned by the negative AIM-HIGH and HPS2-THRIVE outcomes trials [30].

Novelty: Low. The lipid-modifying activity of niacin has been characterized since the 1950s.

Current trajectory: Declining. The negative AIM-HIGH (2011) and HPS2-THRIVE (2014) cardiovascular outcomes trials failed to demonstrate benefit of niacin added to statin therapy, and the FDA withdrew approval for the extended-release niacin/laropiprant combination (Tredaptive). Niacin monotherapy remains available as a dietary supplement and as prescription Niaspan, but clinical enthusiasm has diminished substantially [30].

Side-effect profile: Unfavorable relative to bergamot. Flushing (prostaglandin-mediated cutaneous vasodilation) affects 50 to 80 percent of patients and is the primary cause of discontinuation. Additional adverse events include hepatotoxicity (dose-dependent, particularly with sustained-release formulations), hyperglycemia (worsening of insulin resistance, paradoxically opposite to the insulin-sensitizing effect of bergamot), hyperuricemia, and gastrointestinal discomfort [30].

Overall validation: Moderate. The lipid-modifying efficacy is well established. The cardiovascular outcomes evidence is negative in the statin era (AIM-HIGH, HPS2-THRIVE), though pre-statin era trials (Coronary Drug Project, 1975) demonstrated mortality benefit. The declining trajectory and adverse-event burden reduce the practical validation.

Comparison to bergamot: Bergamot has a substantially more favorable side-effect profile than niacin (no flushing, no hyperglycemia, no hepatotoxicity). Niacin has a larger HDL-C effect but negative cardiovascular outcomes data in the statin era. Bergamot offers insulin-sensitizing effects that are directionally opposite to niacin-induced hyperglycemia. The comparison favors bergamot for metabolic syndrome populations where both lipid and glycemic management are priorities.

12.5 Artichoke Leaf Extract (*Cynara scolymus*)

Mechanism: Artichoke leaf extract contains cynarin and luteolin, which stimulate bile acid synthesis and secretion, increase biliary cholesterol excretion, and modestly inhibit HMGCR. The mechanism is primarily choleretic (bile flow stimulation) with secondary lipid-lowering effects [31].

Effect size: Meta-analyses report LDL-C reductions of 5 to 15 percent and modest triglyceride reductions with artichoke leaf extract at doses of 600 to 2700 mg daily. The effect size is generally smaller than that of bergamot polyphenolic extract [31].

Novelty: Low. The choleretic and hypolipidemic activities of artichoke have been studied since the 1930s.

Current trajectory: Stable. Artichoke leaf extract is widely available as a dietary supplement in the EU and the United States. The wild cardoon (*Cynara cardunculus*), a close relative, has been combined with bergamot extract in the Bergacyn formulation with positive clinical results in NAFLD [15].

Side-effect profile: Very favorable. Mild gastrointestinal effects (flatulence, increased stool frequency) reflecting the choleretic mechanism. Allergic reactions in individuals with Asteraceae sensitivity. No significant hepatotoxicity or drug interactions at standard doses [31].

Overall validation: Moderate. Multiple meta-analyses support modest LDL-C reduction. No cardiovascular outcomes trial. The evidence base is smaller and less rigorous than that for red yeast rice or berberine.

Comparison to bergamot: Bergamot has a larger effect size on LDL-C and offers additional glycemic and AMPK-mediated metabolic benefits that artichoke does not. Artichoke has a favorable side-effect profile comparable to bergamot. The combination of bergamot and artichoke/cardoon (as in Bergacyn) has been clinically validated and is mechanistically complementary, with artichoke contributing choleretic bile acid excretion to bergamot's synthesis inhibition and absorption reduction mechanisms.

12.6 Comparator summary

The five comparators occupy distinct positions in the lipid-modifying nutraceutical landscape. **Red yeast rice** has the strongest clinical validation, including the only positive cardiovascular outcomes trial among nutraceuticals, but faces regulatory restrictions and shares statin adverse effects. **Berberine** has strong clinical evidence with effect sizes comparable to bergamot and offers mechanistically distinct LDL receptor and PCSK9 modulation, but has a more pronounced gastrointestinal adverse-event profile. **Plant sterols** have the strongest regulatory validation (authorized health claims) and the best safety profile, but the smallest effect sizes. **Niacin** produces the largest HDL-C effect but has unfavorable tolerability and negative cardiovascular outcomes data in the statin era. **Artichoke leaf extract** has modest effect sizes and good tolerability but limited evidence depth.

Citrus bergamot extract occupies a distinctive position through its pleiotropic mechanism (AMPK activation, HMGCR protein reduction, NPC1L1 modulation, anti-inflammatory activity), its favorable tolerability profile, its concurrent

glycemic and hepatoprotective effects, and its clinically meaningful LDL-C effect sizes (18 to 36 percent). The principal limitations are the absence of a cardiovascular outcomes trial, the predominantly open-label nature of the early clinical evidence, the limited pharmacokinetic characterization, the CYP3A4 interaction concern from furanocoumarin content, and the dependence on a single geographic source (Calabria) for the reference extract material.

The practical comparison for metabolic syndrome populations, where both lipid and glycemic management are priorities, favors bergamot over niacin (better tolerability, insulin sensitizing versus insulin worsening) and over artichoke (larger effect size, additional glycemic benefit). The comparison with red yeast rice and berberine is more nuanced, with red yeast rice having stronger validation but more regulatory and safety concerns, and berberine having comparable effect sizes but greater gastrointestinal adverse events. Combination strategies (bergamot plus plant sterols, bergamot plus berberine, bergamot plus artichoke/cardoon) are mechanistically rational, clinically explored in some cases, and represent a productive direction for nutraceutical lipid-lowering research.

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