Chapter 10

Plants with Hypolipidaemic Effects from Nigerian Flora

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1. Introduction

Definition: Hyperlipidemia is a heterogeneous group of disorders characterized by high level of lipids (fats) in the bloodstream. These lipids include cholesterol, cholesterol esters, phospholipids, and triglycerides. Lipids are transported in the blood as large 'lipoproteins'. Alternatively, the disease refers to elevated levels of lipids and cholesterol in the blood, or the manifestations of different disorders of lipoprotein metabolism (dyslipidemia).

Causes: Hyperlipidemia could be caused by: (i) Familial combined hypercholesterolemia (ii) Familial hypertriglyceridemia (iii) other disease states such as *insulin and non-insulin dependent diabetes mellitus*, *hypothyroidism*, *Cushing's syndrome*, dysproteinemias, *nephrotic syndrome* and *renal failure*, cholestatic disorders and low thyroid (iv) drugs such as anabolic steroids, beta-blockers, birth control pills and estrogens, corticosteroids, protease inhibitors, retinoids, thiazide diuretics (v) diets like cholesterol intake greater than 300 mg per day, fat intake per total calories greater than 40 %, saturated fat intake per total calories greater than 10 % (vi) life style involving habitual excessive alcohol use, lack of exercise, smoking (vii) risk factors such as advancing age, sex (male), stress and postmenopause.

Classification: Lipoproteins are divided into five major classes, based on density and they include: (i) chylomicrons (ii) very low-density lipoproteins (VLDL) (iii) intermediate-density lipoproteins (IDL) (iv) low-density lipoproteins (LDL) and (v) high-density lipoproteins (HDL). Most triglyceride is transported in chylomicrons or VLDL, while most cholesterol is carried in LDL and HDL. Hyperlipidemia, a major, modifiable risk factor for atherosclerosis and cardiovascular disease, including coronary heart disease (CHD) is classified under (1) Primary hyperlipidemias - are probably genetically based, but the genetic defects are known for only a minority of patients. Examples are (i) primary chylomicronemia- recessive traits of deficiency of lipoprotein lipase or its cofactor (ii) familial hypercholesterolemia- an autosomal

dominant trait, although levels of LDL tend to increase with normal VLDL; familial combined (mixed) hyperlipoproteinemia- elevated levels of VLDL, LDL (iii) familial dysbetalipoproteinemia-increased LDL with increased TG and cholesterol levels (iv) familial hypertriglyceridemia-increased VLDL production with normal or decreased LDL (v) familial mixed hypertriglyceridemia-serum VLDL and chylomicrons are increased. (2) Secondary hyperlipidemia- results from disease states such as Cushing's syndrome, diabetes, liver disorders, renal disorders, thyroid disease, obesity, as well as alcohol consumption, estrogen administration, and other drug-associated changes in lipid metabolism.

Symptoms: Hyperlipidemia usually does not cause symptoms. Very high levels of lipids or triglycerides can cause yellowish nodules of fat in the skin beneath eyes, elbows and knees, and in tendons (xanthomas). Sometimes pain, swelling of organs such as the liver, spleen or pancreas (pancreatitis) or whitish rings around the eye's iris occur. **Diagnosis**: Diagnosis is typically based on medical history, physical examination and most importantly blood test done after overnight fasting. The blood test, measure the levels of lipids in the blood and consist of, a fasting blood test for total cholesterol (TC), LDL (bad cholesterol), HDL (good cholesterol), triglycerides (TG). American Cholesterol Education Program advises that lipids be checked at least once every five years, starting at age 20. However, more frequent or earlier testing is recommended if family history of hyperlipidemia; risk factor or disease that may cause hyperlipidemia; complication that may result from hyperlipidemia exist. Also, the American Academy of Pediatrics recommends lipid screening for children at risk (example, a family history of hyperlipidemia and/or diabetes). Table 1 provides specifications for making a determination.

Cholesterol level	Acceptable	Borderline	High
Total Cholesterol (mg/dl)	<170	170 – 199	≥ 200
LDL Cholesterol (mg/dl)	<110	110 – 129	≥ 130
HDL Cholesterol (mg/dl)	<40	40-59	≥ 60
Total glycerides (mg/dl)	<150	150-200	≥ 200

Table 1. Classification of cholesterol level

Prevalence: (i) A significant percentage of world population has an increased plasma lipid level, resulting in increased risk of coronary heart disease (ii) Ethnic groups adopting a 'western' lifestyle tend to have higher levels of plasma lipids (iii) Men >30 years and women >55 years (in the U.S.) have10 % rise in fasting triglyceride level >200 mg/dl (iv) Severe hypertriglyceridemia (>2000 mg/dl) higher in diabetic patients or patients suffering alcoholism (iv) Lipoprotein lipase deficiency prevalence is much higher in Quebec, Canada. (v) total C and LDL-C rise steadily about 20% in men aged 20 to 50 years, 30% in women aged 20 to 60 years and younger women have lower levels than men while homozygous familial hypercholesterolemia manifests itself from birth (vii) hyperlipidermia is higher among men than women (gender factor) (viii) total cholesterol and LDL-C levels are similar in whites and blacks,

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triglycerides are lower and HDL-C levels tend to be higher in the African-American population. Asian-Indians have the highest risk, Europeans have an intermediate risk while Chinese have the lowest risk (race factor) (ix) familial combined hyperlipidemia inheritance is autosomal dominant and likely to involve one of multiple enetic defects, familial hypertriglyceridemia is most likely inherited as an autosomal dominant defect, lipoprotein lipase deficiency and hepatic lipase deficiency are very rare autosomal recessive conditions hypercholesterolemia in the majority of the general public is attributed to high-fat diets and poorly understood susceptibility and modifier genes (genetics factor). Published data on the prevalence of lipid abnormalities in Nigeria are scanty. This could be attributed to low prevalence of hyperlipidemia in Nigeria prior to occidental lifestyle. Osuji et al, 2012, reported that the current state of dyslipidemia in Nigeria clearly contradicts the previous perceptions. In their report, dsylipidemia was found to be highly prevalent in Nigeria with consistent low HDL-cholesterol and high LDL-c especially amongst the upper social class and people with other risk factors. Other studies reported low HDL-c, with TC/HDL-c to be prevalent in the Northern part of the country while high prevalence of TC, TG and low HDL were observed in the Southern part of the country amongst people of upper social class.

2. Treatment

Dietary intervention: is the primary treatment strategy, but drug therapy may often be added later to augment treatment. The main component of a "heart-healthy" diet is a food pattern that is low in saturated fat and dietary cholesterol and provides adequate energy to support growth and maintain an appropriate weight. Specific dietary recommendations include: (i) decreased intakes of saturated fat- most effective in lowering LDL. Sources include stick margarine, partially hydrogenated oils and fats, hydrogenated peanut butters, commercial bakery products, commercial fried food (e.g., French fries) and high fat animal products (ii) decreased intakes of trans-fatty acids- trans-fatty acids are thought to increase LDL levels nearly as much as saturated fat and appear to lower HDL. (iii) decreased intakes of dietary cholesterol- lead to LDL reduction. Diabetic patients tend to be more sensitive to dietary cholesterol intake, which is only found in animal products (iv) balance the fatty acid composition of diet- polyunsaturated and monounsaturated fatty acids can lower LDL and could be good substitutes for saturated fats (v) increased fiber intakes- soluble fiber can contribute to LDL reduction and is now a formal part of hyperlipidemia dietary recommendations. Common sources of fiber include oats, psyllium, guar gum, pectin, barley, dried beans, fruits, vegetables, cereals, whole grains, and legumes are good sources of soluble fiber (vi) encourage antioxidant food sources such as carotenoids, vitamins C and E and antioxidant-rich foods such as whole grains, citrus fruits, melons, berries and leafy green vegetables rather than supplements (vii) reduce serum homocysteine levels- adequate intakes of folate and vitamins B_6 and B_{12} as well as total fat restriction may keep homocysteine levels low. Food sources of these nutrients include fruits, dark green and leafy vegetables, fortified cereals, whole grains, lean meats and poultry.

Drug Therapy: Currently, there are many classes of medications that may be utilized in the pharmacologic management of hyperlipidemia. They are (1) HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors (statins). The cornerstone of the lipid-lowering therapy in adults has rested with the HMG CoA reductase inhibitors or statins. The use of these drugs has resulted in important reductions in overall cardiovascular morbidity and mortality. Mechanism of action- reduction of cholesterol synthesis in liver; inhibiting the rate-limiting step in endogenous cholesterol synthesis; compensatory increase in synthesis of LDL receptors on hepatic and extra hepatic tissues; increase in hepatic uptake of circulating LDL which decreases plasma LDL cholesterol; increase in HDL, decrease in TGs and vasodilatation and decrease in atherosclerosis. Pharmacological indication: Clinically used in the treatment of all types of hyperlipidemia except those who are homozygous for familial hypercholesterolemia (lack of LDL receptors). Table 2 summarizes the statins and their clinically applications.

Drug	Starting Dose (mg)	FDA-Approved Maximum (mg)	Half-life (hours)	Average Decrease in LDL-C Per Dose (mg:%)
Atorvastatin (lipitor)	10-20	80	14 or 20-30	10:39 20:43 80:60
Fluvastatin (Lescol)	20	80	3	20:22 80:35
Lovastatin (Mevacor)	20	80	2	20:28
Pitavastatin (Livalo)	2	4	12	2:36 4:43
Pravastatin (Pravachol)	40	80	2	40:34 80:37
Rosuvastatin (Crestor)	5-10	40	19	5:45 10:52 40:63
Simvastatin (Zocor)	20	80	4	20:38 80:36-47
Simvastatin/Ezetimibe (Vytorin)	10/10	10/40	22	10/10:45 10/40:55

Table 2. HMG-CoA INHIBITORS

(2) Fibrates (activators of lipoprotein lipase): Mechanism of action- agonists at peroxisome proliferator-activated receptor (PPAR); hydrolysis of VLDL and chylomicrons; decrease in serum TGs; increase clearance of LDL by liver and increase in HDL and expression of genes responsible for increased activity of plasma lipoprotein lipase enzyme. Pharmacological indication: most effective in reduction TGs (hypertriglyceridemia); combined hyperlipidemia (type III) if statins are contraindicated. Typical examples are fenofibrate(prodrug) and gemfibrozil (lopid) (3) Ezetimibe: Mechanism of action- inhibits intestinal cholesterol and

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related phytosterol absorption; decrease in concentration of intrahepatic cholesterol; increase in uptake of circulating LDL; decrease in serum LDL cholesterol levels and compensatory increase in LDL receptors. Pharmacological indication: Effective in hypercholesterolemia together with statins and diet regulation; utilization of ezetimibe along with a statin allows for lower doses of the statin to be used, therefore reducing the likelihood of dose-related side effects of the statin. (4) Nicotinic acid; Niacin (Inhibitor of lipolysis): Mechanism of action- a potent inhibitor of lipolysis in adipose tissues; decreases mobilization of FFAs (major precursor of TGs) to the liver; increases HDL levels; decreases LDL, decreases endothelial dysfunction and thrombosis. Pharmacological indication- Used in the treatment of familial hyperlipidemias (type IIB) (increase in VLDL and LDL); combined with fibrates or cholestyramine in the treatment of hypercholesterolemia (5) Bile acids- Sequestrants(resins): The bile acid binding resins have been felt to be preferred in the pediatric age group as they are not systemically absorbed. Mechanism of action- are anion exchange resins; bind bile acids in the intestine forming complex that leads to loss of bile acids in the stools; increase the conversion of cholesterol into bile acids in the liver; compensatory increase in LDL receptors leading to decreased concentration of intrahepatic cholesterol; increase hepatic uptake of circulating LDL and decrease serum LDL cholesterol levels. Pharmacological indication: Effective in the treatment of type IIA and IIB hyperlipidemias (along with statins when response to statins is inadequate or they are contraindicated); treatment of pruritus in biliary obstruction (as rising from increase in bile acids). Typical examples are cholestyramine, colestipol and colesevelam. (6) Lovaza (Omega-3-acid ethyl ester): Mechanism of action: is unclear; however, proposed mechanisms include decreasing lipogenesis in the liver, increasing plasma lipoprotein lipase activity, and increasing mitochondrial and perixosomal lipase activity. The drug may increase aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and has also been known to prolong bleeding time. Pharmacological indication: is indicated as adjunct therapy to diet in patients with triglyceride levels greater than or equal to 500 mg/dl (hypertriglyceridemia). It provides significant reduction in triglycerides, of approximately 44.9%, making it an ideal drug choice in patients with high triglycerides (7) Fish oil is another common over-the-counter (OTC) product that provides an alternative to the prescription product Lovaza (8) OTC herbal product: (i) Red yeast rice (RYR)- herbal supplements used for lipid-lowering effects. RYR is obtained by fermenting *Monascus purpureus*, a form of yeast, on rice, which is then dried, pulverized, and encapsulated. This process leads to the formation of 14 monacolins, which are compounds that inhibit HMG-CoA reductase. One of the mona-colins, monacolin K (lovastatin or mev-inolin) was the first synthesized HMG-CoA reductase inhibitor. RYR is commercially available in 600-mg capsules (ii) Plant sterols and stanols also assist in the reduction of LDL-C. Plant sterols reduce cholesterol absorption by competing with cholesterol for space within bile salt micelles in the intestinal lumen. The plant stanols, which are the result of the hydrogenation of sterols, are not absorbed as well as sterols. Ingestion of about 2 g per day of plant sterols or stanols, produces LDL-C reduction of 6% to 15%. Prevention: Cardiovascular disease (CVD) is the leading cause of mortality in advance countries, with hyperlipidemia a common risk factor for CVD, in adults having abnormal cholesterol values and elevated low-density lipoprotein (LDL) cholesterol levels. Prevention could be subdivided

into: Primary prevention- (i) initial treatment is diet/exercise and should be given three to six months on dietary therapy prior to beginning medication and longer if lipids are improving and nearing LDL thresholds (ii) obtain cholesterol tests starting at the age of 20 (iii) eat a diet low in total fat, saturated fat, and cholesterol namely eat poultry without the skin, fish, vegetables, most fruits, whole grains, and skim milk (iv) reduce sugar intake (v) eat foods high in soluble fiber (vi) eat more cold water fish and soy products (vii) avoid cigarette smoking (viii) drink alcohol in moderation (two drinks per day for men, one drink per day for women) (ix) avoid overweight (x) exercise regularly and control blood sugar if diabetes is implicated (xi) increase physical activity (xii) consume a diet that contains adequate potassium, calcium, and magnesium to facilitate blood pressure control. Secondary prevention: Measuring lipids in adolescents that have strong family history of two or more coronary heart disease risk factors. In summary, US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III in its guidelines has communicated the importance of early identification of risk, lifestyle modification, and pharmacologic treatment as the mainstay of therapy for hyperlipidemia and in the prevention of cardiovascular-related death.

The Promise of Nigeria Natural Products: Since the recognition of hyperlipiermia, a large number of plant species have been identified as having antihyperlipidermic properties and natural products are part of the current therapy for hyperlipidermia. Numerous natural products with antihyperlipidemic effect have been described in the literature. The objective of this chapter is to summarize the role of Nigeria natural products in the treatment and prevention of hyperlipidermia to date and to highlight specific classes of compounds that possess a requisite level of activity that would be considered worthy of further investigation as potential drug candidate.

3. Discussion

3.1. Antilipidemic agents from Nigeria flora

In Nigeria, traditional medicine has been the most popular means of healthcare from the olden days, before the emergence of alternative medicine in the form of synthetic agents. Traditional medicine can be said to be indigenous and a culture handed over to us by our anscestors as a means of surviving from various ailment obvious in every society. Due to high cost of synthetic drugs and side effects, natural products have become the best alternative strategy for the development of safe antilipidemic drugs. Various natural products both crude and isolated components found from plants are effective remedies for hyperlipidemia cases. Several proves are available in nature, indicating the positive effects of many natural product components that can be employed for the treatment of hyperlipidemia. Ibrahim *et al*, 2013 stated that polyphenols as apigenin, genistein and catechins as well as saponins, sterols, stanols polyunsaturated fatty acids, mucilage and carbohydrates are good examples of agents found to exhibit potent hypocholesterolemic activities. Table3 summarizes the continuous investigations of Nigerian plants used as antihyperlipidemia from ethnopharmacological approach based on the folkloric claims.

Sources	Morphological parts	Comments	References
PerseaAmerican (Avocado pea)	Leaves, methanolic extract	Hypolipidemic activity at 40 mg/kg	Kolawole *et al*., 2012
Garciniakola	Root and seed, normal saline extracts	Hypolipidemic activity at 300-900 mg/kg	Udenze *et al*., 2012
Viscumalbum	Plant parts, methanolic extract	Hypolipidemic activity at 50-100 mg/kg	Oluwatosin *et al*., 2012
Caricapapaya	Seed, aqueous extract	Hypolipidemic activity at 100-400 mg/kg	Nwangwa and Ekhoye 2013
Emilapraetermissa	Leaves, aqueous extract	Hypolipidemic activity	Anaka *et al*., 2013
Cleistopholis patens	Leaves, aqueous extract	Hypolipidemic activity at 400-600 mg/kg	Udem *et al*., 2011
Solanumanguivi, *S. macrocarpum*	Fruit, aqueous extract	Hypolipidemic activity at 20-100 mg/kg	Elekofehiniti *et al*. 2012; Sodipo *et al*., 2011
Annonamuricata	Plant parts, methanolic extract	Hypolipidemic activity	Adeyemi *et al*., 2009
Nauclealatifolia	Root and stem bark, ethanolic extract	Hypolipidemic activity at 100-150 mg/kg	Odey *et al*., 2013
Acalypha torta A. capitata	Leaves, aqueous extract	Hypolipidemic activity at 100-200 mg/kg	Nnodim *et al*, 2011
Scopariadulcis	Plant (herb) parts, methanolic extract	Hypolipidemic activity	Orhue and Nwanze, 2006
Alchorneacordifolia	Leaves, butanolic extract	Hypolipidemic activity at 800 mg/kg	Mohammed *et al*., 2012
Vernonia amygdalina Vernonia amygdalina	Plant parts, methanolic extract; Leaves, ethanolic extract; root, normal saline extract	Hypolipidemic activity Hypolipidemic activity at 100-200 mg/kg	Oluwatosin *et al*., 2008 Igbakin 2009, Owen *et al*., 2011
Moringa oleifera	Leaves, aqueous extract	Hypolipidemic activity at 1 mg/g	Ghasi *et al*., 2000
Clerodendrumcapitalum	Leaves, aqueous extract	Hypolipidemic activity at 100-800 mg/kg	Adenaya *et al*., 2008
Parkiabiglobosa	Plant parts, methanolic extract	Hypolipidemic activity at 30-60 mg/kg	Odetola *et al*., 2006
Citrusparadisi	Seed, methanolic extract	Hypolipidemic activity at 100-600 mg/kg	Adeneye, 2008
Cymbopogoncitrates	Leaves, aqueous extract	Hypolipidemic activity at 125-500 mg/kg	Adeneye & Agbaje, 2007
Catharanthusroseus	Leaves, aqueous extract	Hypolipidemic activity at1 ml/kg	Antia & Okokon, 2005
Albizziachevalieri	Root, aqueous extract	Hypolipidemic activity at 100-300 mg/kg	Saidu *et al*., 2010
Stachytarphelaaugustifolia	Aerial part, methanolic extract	Hypolipidemic activity	Garba *et al*., 2013
Vitexdoniana	Leaves, ethanolic extract	Hypolipidemic activity	Oche *et al*., 2012

Sources	Morphological parts	Comments	References
Morindamorindoides	Root bark, methanolic extract	Hypolipidemic activity	Olukunle *et al*., 2012
Arachishypogaea	Plant parts, aqueous extract	Hypolipidemic activity at 175 mg/kg	Bilbis *et al*., 2002
"Ata-Ofa' (polyherbal tea)	Leaves, methanolic extract	Hypolipidemic activity at 50 mg/kg	Atawodi, 2001
Xylopiaaethiopica	Seed, methanolic extract	Hypolipidemic activity at 250 mg/kg	Nwozo *et al*., 2011
Parinaripolyandra	Fruit, ethanolic extract	Hypolipidemic activity at 50-250 mg/kg	Abolaji *et al*., 2007
Telfairia occidentalis	Plant parts, methanolic extract	Hypolipidemic activity	Adaramoye *et al*., 2007
Curcuma longa	methanol extract of the rhizomes	hypoglycemic and hypolipidemic acitivity 100 mg/kg	Nwozo *et al*, 2009.
Spondiamombia	Aqueous leave extract	Lipid lowering effect at the doses of 250, 500and 750 mg/kg	Igwe *et al*, 2008
Crotonzambesicus	Ethanolic leaf extract	Lipid lowering effect	Ofusori *et al*, 2012.
Momordicacharantia Linn	Methanolic extract of the fruits	Anti-Diabetic and Hypolipidemic Effects at the doses of 200, 400 and 600 mg/kg	Kolawole and Ayankunle, 2012.
Bauhiniathoningii	Aqueous crude extract	Hypoglycemic and lipidemic effecte	Ojezele and Abatan, 2011.
Cajanuscajan	Methanolic leaf extract	Antioxidant and hypolipidemic activity at the dose of 200 mg/kg	Akinloye and Solanke 2011.
Jatrophatanjorensis	Methanolic leaf extract	Serum lipid profile and phytochemical composition at 100, 200 and 500mg/kg dose ranges	Oluwole *et al,* 2011.
Melantherascandens	Ethanolic leaf extract	Antidiabetic and hypolipidemic activities at the doses of 37, 74 &111 mg/kg	Akpan *et al*, 2012.
Ricinuscommunis	Aqueous root extract	Hypoglycaemic potential, lipid profile effects At a dose of 500mg/kg	Matthew *et al*, 2012.

Table 3. Medicinal plants investigated in Nigeria for use as Antihypolipidemic agent

These plants have been identified, authenticated and investigated from Nigeria flora against hyperlipidemia, using pharmacological validated animal models. They all have levels and with some levels of increase in LDL, TC, TG and decrease in HDL. Furthermore, there has been recent interest on the research towards hyperlipidemia due to its obvious relationship with

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diabetes and other ailments like cushing's syndrome, renal disorder, pregnancy, polycystic ovary syndrome, underactive thyroid gland etc. Hyperlipidemia arising from high serum triglyceride or total cholesterol concentration or both has been reported in diabetic and hypertensive patients. Diabetics have been reported to be more prone to cardiovascular diseases including hypertension than non-diabetics (Bilbis et al, 2002). An overview of 40 medicinal plant species from Nigerian indigenous plants reported to have hypolipidemic effects are presented. Most of the reported hypolipidemic effects were on crude extracts and active constituents. Above 30 % of the investigated plant parts had effects on both lipid profile and glyceamic index. However, much still needs to be done on several phytoconstituents of these plants, as well as conduct clinical research on active constituents derived from them, especially in the determination of their levels of toxicity. Other Nigerian plants claimed to have positive effects on lipid profile but found to act as soup thickeners are yet to be investigated. The reported Nigerian plants in Table 3 are rich in soluble and dietary fibres (examples, legumes, fruits and vegetables) and if found to have minimal toxicities, can be incorporated into dietary supplements. According to Ibrahim *et al*, (2013), the major advantage of natural hypolipidemic drugs over synthetic drugs is that many natural drugs exhibit their hypolipidemic activity by different mechanisms. Plants are known to have a striking potential in the management of lipid metabolism and providing better therapeutic effects as an alternative medicine.

4. Conclusion

The use of herbal or natural medicines for the treatment of various disorders has a long and extensive history. The reported plants have the potential to act as lipid-lowering agents with minimal side effects (advantage over currently synthetic drugs) and thus could find their way onto the world market as alternatives to prescribed drugs currently available to treat hyperlipidermia. Most of the studies were carried out with crude extract and administered orally. The principal families in which such activity has been reported are Acanthaceae, Apiaceae, Asteraceae, Azoaceae, Combretaceae, Cucurbitaceae, Euphorbiaceae, Fabaceae, Lamiaceae, Liliaceae, Malvaceae, Myrtaceae, Rubiaceae, Rutaceae and Zingiberaceae, Finally, all the plant species appear to be promising as hypolipidemic agents with activity mediated through various mechanisms.

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