REVIEW

Immunomodulatory Role of Plants and Their Constituents on the Management of Metabolic Disorders: An Evidence-Based Review

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Abstract: The relationship between the immune system and metabolic diseases is complex and increasingly recognized as critical to understanding conditions like obesity, diabetes, and cardiovascular diseases. Modulation of the immune system in patients with metabolic disorders can offer several potential benefits. While the salutary impact of plant-derived bioactive compounds on metabolic and immune functions is acknowledged, there is a paucity of comprehensive reviews on the multifaceted and synergistic mechanisms through which these effects are mediated. This review elucidates the therapeutic potential of phytochemical formulations in ameliorating metabolic disorders and delineates their mechanistic implications on relevant biomarkers and immune modulation. Our analysis reveals a predominance of plant species, including *Boswellia serrata*, *Cinnamomum cassia*, *Citrus bergamia*, *Coffea arabica*, *Ficus racemosa*, *Momordica charantia*, *Morus Alba*, and *Trigonella foenum-graecum*, that have undergone clinical evaluation and have been substantiated to confer both metabolic and immunological benefits. The phytoconstituents contained in these plants exert their effects through a range of mechanisms, such as improving glucose regulation, reducing inflammatory responses, and modulating immune system. As such, these findings hold considerable promise for clinical and therapeutic translation and necessitate further empirical validation through randomized controlled trials and mechanistic elucidations to affirm the safety and efficacy of herbal formulations.

Keywords: metabolic disease, immune system, phytoconstituents

Introduction

Metabolic disorders encompass a spectrum of conditions that disrupt normal metabolic processes, resulting in various health problems, including type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome (MetS).[1,2] Furthermore, the pathologies of metabolic diseases are intricate and multifactorial, and elevate the risk for cardiovascular disease (CVD).[3] In their recent article, Saeedi et al reported that 9.3% of the global population (463 million people) was estimated to suffer DM, and this number is expected to increase to 10.2% (578 million) by 2030 and further to 10.9% by 2045.[4] Concurrently, the global prevalence of obesity continues to escalate over the past 50 years, with its consequences encompassing the exacerbation of chronic conditions such as T2DM, coronary heart disease (CHD), hypertension, osteoarthritis, and cancers.[3,5,6]

Metabolic diseases and CVD tend to be of long duration and slow progression (chronic) comprising several metabolic disorders due to the involvement of various physiological processes in their development and progression. They are usually the result of genetic, environmental, or lifestyle factors that interfere with the normal functioning of the body's metabolic pathways. Over time, metabolic disorders manifest as a spectrum of intermediate phenotypes, culminating in metabolic syndrome elevating the risk for T2DM and atherosclerotic conditions.[7] People with metabolic disorders can be more susceptible to infectious diseases due to several factors such as a weakened immune system, treatment-related

513

immunosuppression, co-existing health conditions, and overlapping risk factors. Many metabolic conditions, including DM, cancer, and chronic kidney disease (CKD), compromise the immune system, thereby the body is difficult to fight off infections.[8]

Concerning the recent pandemic, data indicate a correlation between the severity of COVID-19 and the presence of DM and hyperglycemia. People with DM have been reported to face an augmented risk of SARS-CoV-2 infection, with inadequate glycemic control intensifying treatment and hospitalization necessities and fatality rates. Hyperglycemia, coupled with other risk factors, may tweak immune and inflammatory responses, rendering individuals susceptible to severe COVID-19 manifestations. Complications associated with DM, such as hypertension, obesity, heart failure, and CKDs, further increased COVID-19 mortality risks.[9,10] Notably, the COVID-19 pandemic underscores cardiac patients as particularly vulnerable, with the viral infection instigating cardiovascular complications like myocarditis, arrhythmias, cardiogenic shocks, heart failures, and thromboembolic episodes.[11]

Current treatments for metabolic syndrome (MetS) disorders focus on managing individual risk factors to reduce the overall risk of developing related complications, such as CVD and T2DM. The main components of treatment include lifestyle modifications and pharmacological intervention. However, these treatments have revealed their limitations.[11] Adopting a healthier lifestyle is the cornerstone of MetS treatment. This includes a balanced diet, regular physical activity, weight loss, smoking cessation, and moderate alcohol consumption.[12] Embracing healthier lifestyles, characterized by balanced diets, consistent physical activity, weight management, smoking cessation, and moderate consumption of alcohol, is pivotal for MetS management.[11] Notably, dietary choices significantly influence metabolic disorder etiology, rendering them instrumental in CVD, MetS, and T2DM prevention strategies.[13–16]

Recently, the therapeutic potential of natural foods in MetS management has garnered significant interest.[16–18] Clinical and epidemiological research underscores a diet dominated by plant-based foods as beneficial for metabolic homeostasis and highlights the potential of fruit and vegetable consumption in curbing CVD onset, attributed to phytoconstituents like polyphenols and flavonoids. These are renowned for their antioxidant and anti-inflammatory activities.[19–21] Those bioactive compounds are predicted to act synergistically via various biological pathways to reduce chronic disease manifestation.[22] A sustained dietary regimen lacking these essential components emerges as a primary factor leading to the dysregulation of metabolic homeostasis.[19]

In this context, it is important to understand how bioactive compounds act synergistically on metabolic homeostasis and immune system which can play a fundamental role in the prevention and clinical management of metabolic disorders. Several clinical trials have evaluated the efficacy of plant-based or herbal preparations for metabolic disorders and their risk factors.[2,16,19,20,23,24] Furthermore, the mechanism of actions of bioactive compounds on metabolic biomarkers has also been reported.[25,26] However, their potential on how those bioactive compounds exhibit multiple and synergistic effects on metabolic and immune systems is not thoroughly discussed yet. In this review, we discuss the efficacy of plant-based or herbal preparations for metabolic disorders and the mechanisms of actions of their bioactive compounds on metabolic biomarkers. This review delves into the potency of botanical and herbal formulations for metabolic irregularities and the operational mechanisms of their inherent bioactive constituents on metabolic indicators. We subsequently offer an incisive discourse on the prospective contributions of these natural entities to immune system modulation, positing them as a potential supplementary therapy to mitigate the risks and improve the quality of life of individuals with metabolic disorders.

Materials and Methods

The information retrieval was carried out through the PubMed database due to its esteemed results yielding the most relevant human clinical trials. The articles were searched using the keywords "metabolic disorders" OR "metabolic disease" AND "medicinal plants" OR "bioactive compounds" AND "clinical trials" (N = 124).

Study Design

A comprehensive literature review was conducted, where sources were screened based on their titles and abstracts. Studies that met the eligibility criteria and were available in full text were chosen for inclusion. Duplicates, unrelated articles, study methodologies, and clinical studies involving pediatric populations were excluded during the filtering
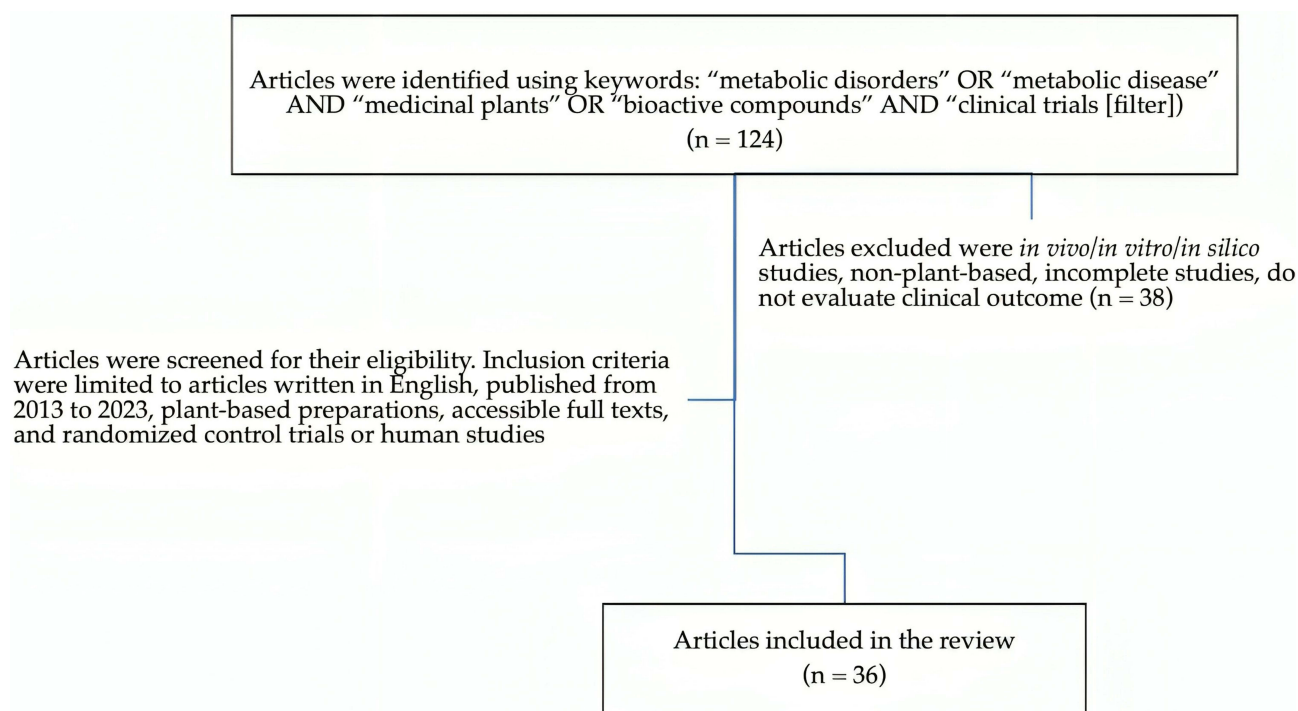
Articles were identified using keywords: "metabolic disorders" OR "metabolic disease" AND "medicinal plants" OR "bioactive compounds" AND "clinical trials [filter])
(n = 124)

Articles excluded were *in vivo/in vitro/in silico* studies, non-plant-based, incomplete studies, do not evaluate clinical outcome (n = 38)

Articles were screened for their eligibility. Inclusion criteria were limited to articles written in English, published from 2013 to 2023, plant-based preparations, accessible full texts, and randomized control trials or human studies

Articles included in the review
(n = 36)

Figure 1 The study design of the evidence-based review.

process. The final selection of articles was determined after examining reference lists, and evaluations were made based on the aforementioned criteria. The incorporated studies exhibited variability regarding sample sizes and clinical results. The derived data are presented narratively, leading to the resultant conclusions. The process of selecting suitable studies is depicted in Figure 1.

Literature Search and Study Selection

In the preliminary electronic search, 124 prospective studies were examined. Following the elimination of duplicates, the residual articles were evaluated for pertinence based on the predefined inclusion parameters for this review. Thirty-six trials with plant-based preparations as a treatment for metabolic diseases and their risk factors were identified and further examined as full texts. The characteristics of the included trials are tabulated in Table 1.

Results

The Role of Plant-Based Diets and Phytochemicals in Alleviating Metabolic Disorders

Among the thirty-six eligible studies, ten studies enrolled patients with either T2DM or prediabetes,[13,27–34,49] seven studies enrolled overweight or obese subjects,[14–16,36,42,45,47] three studies enrolled patients with metabolic syndrome or their risk factors,[19,20,50] three studies evaluated patients dyslipidemia,[12,21,35] two studies enrolled patients with hepatic steatosis or non-alcoholic fatty liver disease (NAFLD),[39,41] other studies enrolled patients with CVD or CVD risk factors,[37,40] diabetic nephropathy,[38] and healthy volunteers.[1,22,25,26,43,44,46,48]

The primary intervention for metabolic disorders entails dietary and lifestyle modifications. It is well established that enhancing dietary practices—including reduced caloric consumption in instances of overweight and obesity and decreased intake of sodium, saturated fats, cholesterol, and simple sugars—can facilitate the clinical management of MetS-associated comorbidities. Several studies have delineated the positive outcomes of plant-based dietary regimens on parameters such as glucose concentrations, lipid profiles, body mass, blood pressure, and inflammatory indices (as shown in Table 1). In detail, 15 of the 36 studies focused on individuals with hyperglycemia and/or obesity, and 2 of the 36 centered on healthy participants, all of which noted metabolic improvements, including reductions in glycated

Table 1 Characteristics of the Included Trials

Ref., Year	Metabolic Diseases	Design of Study*	Number of Subjects	Subject Characteristics	Clinical Features	Plants/Herbal Preparation/ Bioactive Compounds	Control Drugs	Duration of Therapy	Clinical Outcomes
Butacnum et al, 2017[27]	T2DM	RCT, double-blind, placebo-controlled, and crossover	24	• Men and women • Aged 20–60 years old • BMI 25.0–28.7 kg/m^2	• FBG for normal group 70–100 mg/dL • FBG for pre-diabetic group 100–125 mg/dL • No diabetes, kidney or liver disease.	Black tea (Camellia sinensis)	N/a	2 hours	• Ingestion of black tea enriched with BTPP has been observed to markedly reduce postprandial glucose levels following sucrose consumption in individuals with normal glycemic control as well as in those with pre-diabetic conditions
Mansour et al, 2021[28]	NAFLD and T2DM	RCT, double-blind, and placebo-controlled	101	• Men and women • Aged 30–53 years old	• T2DM and NAFLD (controlled attenuation parameter score of 260 or more)	Coffea arabica (chlorogenic acid, caffeine, and their combination)	N/a	6 months	• Neither chlorogenic acid nor caffeine demonstrated a significant advantage over placebo in reducing hepatic fat accumulation, liver stiffness, or in improving other liver-associated outcomes in patients diagnosed with diabetes concomitant with NAFLD • Lower level of total cholesterol In comparison to the placebo group, the caffeine cohort exhibited a statistically significant reduction in total cholesterol levels (p = 0.04), while the group receiving both chlorogenic acid and caffeine demonstrated a significant elevation in insulin levels (p = 0.01)
Geberemeskel et al, 2019[29]	T2DM	RCT	114	• Men and women • Aged 35–75 years old	• Newly diagnosed T2DM patients without any significant diabetes complication	Trigonella foenum-graecum seed powder	Metformin	1 month	• The intervention group exhibited a marked 13.6% decline in serum total cholesterol (TC), a 23.53% reduction in serum triglycerides (TG), and a notable 21.7% elevation in serum high-density lipoprotein cholesterol (HDL-C) levels • Serum low-density lipoprotein cholesterol (LDL-C) levels demonstrated a significant decline of 23.4%, with no reported adverse events
Chusak et al, 2020[13]	T2DM	RCT and crossover	20	• Men and women • Aged 20–40 years old • BMI 18.5–22.9 kg/m^2	• FBG <100 mg/dL, • A fasting TC <200 mg/dL • A fasting TG <150 mg/dL • A fasting LDL-c <130 mg/dL • Free of serious illness	Anthocyanin-rich rice-berry rice	N/a	3-time visits with intervals of 4–8 weeks for each visit	• Intake of RRB led to a notable reduction in both postprandial (PP) plasma glucose and insulin levels
Gul-e-Rana et al, 2013[30]	T2DM	Pre- and post-analysis clinical trial	50	• Men and women • Adults	• Diabetic patients taking oral hypoglycemic drugs	Ficus racemosa bark	N/a	15 days	• The combined treatment reduced blood glucose (BG) levels, with a marked decline observed in male participants 1.5 hours post-administration

Huang et al, 2017[31]	T2DM	RCT, double-blind, and placebo-controlled	41	• Aged 20–75 years • BMI ≥ 23 kg/m²	• T2DM • Treated with ≥3 classes of OHAs with persistent (>6 months) poorly controlled glycemia (HbA1c >7.0% or 53 mmol/mol)	SLBZS consists of Radix Ginseng, Poria, Rhizoma Atractylodis macrocephalae, Semen Lablab album, Rhizoma Dioscoreae, Embryo Nelumbinis, Radix Platycodonis, Semen Coicis, Fructus Amomi, Fructus Jujubae, and Radix Glycyrrhizae	N/a	12 Weeks	• YH1, when combined with oral hypoglycemic agents (OHAs), augments hypoglycemic activity and enhances β-cell function in overweight/obese type 2 diabetes patients with poor glycemic control. • As an adjunctive therapy to OHAs, YH1 is safe and offers advantages in weight management and lipid metabolic regulation.
Krawinkel et al, 2018[32]	T2DM	RCT, single-blind, placebo-controlled, and crossover	52	• Aged 30–65 years old • Waist circumference >80 cm for women and >90 cm for men • BMI 27–35 kg/m²,	• Fasting plasma glucose (FPG) 100–125 mg/dL • HbA1c-values 5.7–7.5% (39–58 mmol/mol) • BP 90/60–160/110 mmHg	Bitter gourd (*Momordica charantia*) powder	N/a	16 weeks (8 weeks/period)	• The CROS analysis indicated a notable variation in the FPG change of 0.31 mmol/L (5.6 mg/dL) (t= −2.23, p=0.031, r=0.326) accompanied by a trend represented by R²=0.42387.
Senadheera et al, 2015[33]	T2DM	RCT and crossover	35	• Aged 35–70 years • Currently not using Scoparia dulcis extract/ porridge	• T2DM • Mild and moderate diabetes (FBG 126–300 mg/dL) • Not currently using Scoparia dulcis extract/ porridge	*Scoparia dulcis* porridge	Normal breakfast except a green leafy porridge	2 period (3 months/period)	• Demonstrated a decrease in fasting blood glucose and HbA1c concentrations in type 2 diabetic patients without any elevation in liver enzymes, creatinine, urea, or CRP
Shokoohi et al, 2017[33]	T2DM	RCT, double-blind, placebo-controlled, and crossover	86	• Women • Aged 40–60 years old	• T2DM • Fasting serum glucose level 150–180 mg/dL • Blood glycosylated hemoglobin levels between 7.5% and 8.5% • Low-density lipoprotein cholesterol >100 mg/dL • Daily oral intake of not more than 10 mg glyburide and 1000 mg metformin at maximum	*Terminalia chebula* fruit extract (200 mg), *Commiphora mukul* (200 mg), and *C. myrrha* oleo-gum-resin (200 mg)	N/a	3 months	• Endpoint measurements indicated a significant reduction in fasting blood glucose, total cholesterol, and low-density lipoprotein cholesterol, coupled with a notable elevation in high-density lipoprotein cholesterol levels when juxtaposed with both placebo and baseline values.
Khalili et al, 2017[34]	T2DM	RCT, double-blind, and placebo-controlled	60	• Men and women • Aged 40–60 years old	• T2DM with fasting blood glucose level from 150 to 180 mg/dL • Glycosylated hemoglobin level from 7.5% to 8.5% • On oral antihyperglycemic drugs	A mixed herbal formulation (*Silybum marianum* (L) Gaertn (milk thistle) seeds, *Urtica dioica* L (nettle) leaves, and *Boswellia serrata* (olibanum gum))	N/a	90 days	• A notable decline in FBG levels was consistently observed in the active drug cohort throughout the investigation (P = 0.003) • Comparative analyses revealed a statistically significant reduction in the average HbA1c value for the active drug group as opposed to the placebo group (P < 0.001)

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Table 1 (Continued).

Ref., Year	Metabolic Diseases	Design of Study*	Number of Subjects	Subject Characteristics	Clinical Features	Plants/Herbal Preparation/ Bioactive Compounds	Control Drugs	Duration of Therapy	Clinical Outcomes
Sola et al,2014[12]	Hyperlipidemia (CVD)	RCT, double-blind, placebo-controlled, two-arm, and multicenter	102	• Community-dwelling • Men and women • Aged >18 years old	• Mild-moderately elevated LDL-c 130 mg/dL-189 mg/dL	Armolipid Plus (red yeast rice extract, policosanol, berberine, folic acid, coenzyme Q10, and astaxanthin)	N/a	12 weeks	• Decline in LDL-C concentrations alongside reductions in TC/HDL-C and ApoB/ApoA1 ratios, concomitant with an elevation in Apo A1 levels
Tariq et al,2016[35]	Hyperlipidemia	Pre- and post-analysis clinical trial	30	• Men • 25–40 years old • No diagnosed with heart disease	• Mild hypercholesterolemic; • No diagnosed with heart disease	*Curcuma zedoaria* Roscoe	N/a	60 days	• Intake of C. zedoaria was associated with a notable 6.8% elevation in HDL-c levels, accompanied by a suggestive decline of 5.6% in serum LDL-c and 12.5% in TG concentrations
Chiu et al,2017[21]	Hyperlipidemia	RCT and placebo-controlled	60	• Men and women • 18–53 years old	• Mild hypercholesterolemia (serum cholesterol 170–200 mg/dL) • Without any metabolic disorder	Prune Essence Concentrate (PEC)	N/a	4 weeks with 2 weeks of follow-up without PEC consumption	• Intake of PEC (I and II) for 4 weeks substantially ameliorated (p < 0.05) the colony number of Bifidobacterium spp. (1.18- and 1.19-fold) and Lactobacillus spp. (1.07- and 1.16-fold), but markedly lowered (p < 0.05) the colony number of Clostridium perfringens (5.97 and 8.35%) and Escherichia coli (6.25 and 9.38%) • The total cholesterol (TC; 5.90 and 6.99%) levels and LDL-c (6.68 and 6.53%) were significantly reduced (p < 0.05) • No change in other lipid parameters
Machado et al,2021[14]	Diseases associated with excess body weight	RCT, double-blind, parallel, placebo-controlled, and two-arm	26	• Men and women • Aged 20–45 years old • BMI 25–35 kg/m² • Consumed regular breakfast • Had low physical activity level; and dietary restraint ≤ 14	• Obesity or overweight	Yacon flour	N/a	6 Weeks	• There was an elevation in plasma total antioxidant capacity • Protein carbonyl concentrations witnessed a reduction
Basu et al, 2021[15]	Obesity and Hyperlipidemia	RCT, double-blind, crossover, and multicenter	33	• Adult • Men and women	• Elevated LDL-c >116 mg/dL	Strawberry powders	Control	14 weeks	• There was a notable enhancement in insulin resistance, lipid particle profiles, and serum PAI-1 among obese adults presenting with elevated serum LDL-C
Ryu et al, 2016[16]	MetS	RCT, double-blind, placebo-controlled, and parallel	50	• Aged 35–65 years old • BMI 23–27 kg/m²	• Mild metabolic syndrome • TG ≥150 mg/dL • HDL-c <40 mg/dL and <50 mg/dL (female) • FBG ≥95 mg/dL	Pterocarpan-High Soybean Leaf Extract	N/a	12 weeks	• Induced modifications in fasting blood and plasma glucose, HbA1c, plasma lipid concentrations, and the expression of inflammation-associated genes in peripheral blood mononuclear cells (PBMCs)

Hochkogler et al, 2018[36]	Obesity	RCT, open, and crossover	26	• Men • Aged 21–43 years old • BMI 25–32 kg/m²) • Not consuming alcohol, tobacco, or drug abuse	• Metabolically healthy	Cinnamyl Isobutyrate	N/a	2 hours	• Observed reductions in ad libitum energy consumption following a standardized breakfast correlated with diminished postprandial plasma glucose concentrations
Johnson et al, 2020[19]	MetS	RCT, single-blind, placebo-controlled, parallel-arm, and pilot	19	• Men and Women • Aged 20–40 years old	• Had three or more of the MetS diagnostic criteria according to the American Heart Association and the National Heart, Lung, and Blood Institute	Cherry juice	N/a	12 weeks	• Oxidized low-density lipoprotein and soluble vascular cell adhesion molecule-1 levels were notably reduced compared to the control, with p-values of 0.047 and 0.036, respectively
Franck et al, 2020[20]	MetS	RCT and double-blind	59	• Men or pre-menopausal women • Caucasian • Aged 18–60 years old • BMI 25–40 kg/m²	• Meet at least one of the following criteria: • TG > 1.35 mmol/L, or • Insulin concentration >42 pmol/L	Raspberry	Control (maintain their health and food habits stable for an 8-week period)	8 weeks	• Decreased postprandial hyperglycemia, hypertriglyceridemia, and inflammatory markers (IL-6 and TNF-α), along with a reduction in systolic blood pressure (SBP)
Kitada et al, 2017[37]	MetS	Investigator-initiated RCT, double-blind, and placebo-controlled	39	• Men or women • Aged 20–70 years old	• Routine clinical biochemistry data is measured as a baseline	Passion Fruit (*Passiflora edulis*) Seeds (picceatanol)	N/a	8 weeks	• Improve metabolic health, including insulin sensitivity, BP, and HR, in overweight men.
Tindall et al,2020[37]	CVDs	RCT and crossover	46	• Men and women • Aged 30–65 years old • BMI 25.0–39.9 kg/m²	• Elevated BP (120–159/80–99 mmHg) • Increased LDL-c (128–177 mg/dL for men and 121–172 mg/dL for women)	Walnuts	N/a	2 weeks	• Compared to baseline measurements, there were notable decreases in brachial and central mean arterial pressure, central diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, and the TC to HDL-C ratio
Taghizadeh et al, 2017[38]	Diabetic Nephropathy	RCT, double-blind, and placebo-controlled	60	• Aged 45 to 85 years old	• Diabetic kidney disease with a proteinuria level greater than 0.3 g/24 h, with or without elevation of serum creatinine levels)	Mulberry extract	N/a	12 weeks	• Significant declines were observed in serum triglycerides (TG) (P = 0.03) and very-low-density lipoprotein cholesterol (VLDL-c) (P = 0.03). • Elevation in high-density lipoprotein cholesterol (HDL-c) (P = 0.03), serum high-sensitivity C-reactive protein (P = 0.02), plasma glutathione (P = 0.005), and malondialdehyde (P < 0.001)
Ferro et al,2020[39]	NAFLD	RCT and double-blind	94	• Men and women • Aged 30–75 years old	• Hepatic steatosis	Bergamot (*Citrus bergamia*) polyphenol fraction and *Cynara cardunculus* extract	N/a	6 weeks	• Over a six-week period, adults with fatty liver exhibited a reduction in serum uric acid levels

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Table 1 (Continued).

Ref., Year	Metabolic Diseases	Design of Study*	Number of Subjects	Subject Characteristics	Clinical Features	Plants/Herbal Preparation/ Bioactive Compounds	Control Drugs	Duration of Therapy	Clinical Outcomes
Crescenti et al, 2013[40]	CVDs	RCT	214	• Community-dwelling men and women • aged >20 years old • With a smoking habit	• Pre-hypertensive condition and Stage 1 (SBP: 120–159 mmHg • DBP: 80–99 mmHg); • LDL-c between 130 mg/dL - 89 mg/dL • Minimum one other major CVD risk factor such as age >45 years in men and >55 in women, low HDL-c	Cocoa	An isocaloric diet in which the percentage of saturated fatty acids in the diet was 13% of total energy	14 days	• Significantly reduced the DNA methylation levels (2.991±0.366 vs 3.909±0.380, P<0.001)
Shidfar et al, 2018[41]	Obesity	RCT and single-blind	50	• Aged 20–65 years old • BMI 25–40 kg/m^2 • Not taking hepato-toxic medicines • Not consuming of alcohol ≥30 gr/d • Not in pregnant condition or lactation • Not smoking • Not taking mineral and multivitamin supplements • Not taking olive products and lipid-lowering medicines in the last three months.	• NAFLD patient with the increase of the AST and ALT enzymes (U/L <30 in men and <20 in women) • Not having CVD • Not in diabetic condition	Olive oil	Normal consumption of oil (compared to the test group)	12 weeks	• The control group exhibited a notable decline in ALT enzyme levels (P = 0.004). Meanwhile, participants in the olive oil group displayed a decrease in both enzymes relative to initial measurements (P < 0.01) • Significant difference between the two groups (P < 0.02) in ALT and AST levels were observed
Sanchez-Rodriguez et al, 2018[1]	MetS	RCT, double-blind, parallel, placebo-controlled, and two-arm	53	• Men and women • Aged 20–50 years old	• Healthy	Olive oil	N/a	6 weeks (± 5 days)	• HDL-C levels showed an elevation in female participants; however, no discernible differences were observed following the three interventions • There was an enhancement in a biomarker indicative of endothelial function, noted both in vivo and ex vivo
Hongu et al, 2014[42]	Obesity	RCT and double-blind	24	• Men and women • Aged 21–50 years old • BMI 29–35 kg/m^2 • No weight loss of >5 kg in the last 3 months	• Healthy	Rice bran and plant sterols	N/a	8 weeks	• A notable reduction in the levels of TC and LDL-C was observed between the groups. Additionally, there was a significant decline in SBP when compared to baseline measurements

Rita et al, 2022[43]	T2DM	RCT and blind to the researcher who performed the statistical analysis	31	• Men and women • Aged 18–40 years old	• Healthy • FBG <126 mg/dL	*Adansonia digitata* L. (Baobab aqueous extract)	N/a	1 day (Sampling in 30, 60, 90, 120 minutes)	• Reduced glycemia incremental AUC
Estevez-Santiago et al, 2019[22]	CVD risk factors	Parallel study	72	• Women • Aged (50–70 years) • BMI 25–33 kg/m^2 • Amenorrhea (>2y)	Healthy	Anthocyanins, xanthophylls (lutein + zeaxanthin)	N/a	8 months	• Following 8 months of treatment with A+X, there was a marked reduction in plasma glucose levels. Concurrently, a rise in plasma ferric reducing anti-oxidant power was observed, although no synergistic interaction was discernible between the bioactives in the two groups
Martini et al, 2021[44]	CVD	RCT, crossover, and three-arm	21	• Aged >18 years • BMI 18–25 kg/m^2 • Regular consumers of 1–5 cups of coffee per day.	• Healthy	Coffea arabica (chlorogenic acid, caffeine)	N/a	1 month	• The consumption of coffee or cocoa-based products yielded no discernible impact on cardiometabolic markers
Nilsson et al, 2017[45]	MetS	RCT and crossover	46	• Non-smokers • Aged 50–70 years old • Normal to slightly increased BMI (28 kg/m^2)	• Healthy	A mixture of Swedish berries (polyphenols and carotenoids)	N/a	5 weeks	• The intervention utilizing berries led to a reduction in TC and LDL-C levels relative to the baseline values (both P<0.05). Furthermore, when compared to the control beverage, these reductions were statistically significant, with P-values of <0.005 for TC and <0.01 for LDL-C • Participants exhibited enhanced performance in the working memory test subsequent to consuming the berry beverage in contrast to post-consumption of the control beverage (P<0.05)
Vincellette et al,[26]	Hyperglycemia	RCT, placebo-controlled, double-blind, and crossover	17	• Aged 21–25 years old • BMI 23.5 ± 3.2 kg/m^2	• Healthy	Watermelon juice	N/a	2 weeks	• The postprandial flow-mediated dilation exhibited a higher area under the curve (AUC) (P = 0.03), as did the AUC of microvascular blood (P = 0.01). Additionally, there was a significant elevation in tissue oxygen saturation (StO2%) to 65.9 ± 1.7%. Conversely, the slope related to ischemic-reperfusion remained unaffected by the treatment (P = 0.83)
Valderas-Martinez et al, 2016[25]	CVD	RCT, open, crossover, and prospective	40	• Non-smokers • not receiving medication or vitamin supplements	• Healthy	Tomato sauce with olive oil	Control	14 days	• Tomato sauce augmented with refined olive oil may modulate the lipid profile and influence soluble inflammatory biomarkers associated with the initiation and progression of atherosclerosis.

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Table 1 (Continued).

Ref., Year	Metabolic Diseases	Design of Study*	Number of Subjects	Subject Characteristics	Clinical Features	Plants/Herbal Preparation/ Bioactive Compounds	Control Drugs	Duration of Therapy	Clinical Outcomes
de Morais Junior et al, 2020[46]	Hypertriglyceridemia	RCT, double-blind, placebo-controlled, and crossover	14	• Young women • Aged 18 to 25 years old	• Healthy	EGCG	N/a	Acute (90 and 120 min after the meal)	• EGCG moderated postprandial triglyceride (TG) and glucose levels; however, it adversely influenced HDL-C subsequent to the consumption of a high-fat fast-food meal
Lopez et al, 2017[47]	Obesity	RCT, double-blind, placebo-controlled, parallel-groups design, and single-center	105	• Overweight; men or women • Aged ≥35 to ≤70 years old	• Normally active or judged to be in good health on the basis of medical history and physical examination	T. chebula fruit	N/a	84 days (14 weeks period)	• Relative to the placebo, the treatment notably ameliorated various parameters: mKOOS global scores (P = 0.023), both total and physical function dimensions of mWOMA, VAS indices for Knee Discomfort (P = 0.001), VAS evaluations for systemic joint functionality (P < 0.029), VAS measurements reflecting reduced knee joint soreness (P = 0.022), AyuFlex2 (P = 0.043), the distance traversed during the 6-minute walk assessment (P = 0.047), and the post-walk VAS discomfort scores (P = 0.026). Additionally, there was a suggestive decline in COMP levels, although this did not reach statistical significance (P = 0.104). • Throughout the investigation, all safety biomarkers remained within the established normal range
Kishimoto et al, 2023[48]	CVD risk factors	RCT, double-blind, placebo-controlled, and crossover	23	• Women • Aged 20–35 years old	• Healthy	Strawberry beverage (500 g)	N/a	2 sessions (separated by a 4-week washout period)	• Post ingestion of the strawberry beverage, there was a notable elevation in the serum concentrations of both vitamin C and folate (P < 0.001). The zenith of these levels was observed at the 2-hour mark, recording peak concentrations of 15.0 ± 2.5 µg/mL for vitamin C and 14.4 ± 7.0 ng/mL for folate

Notes: *Not all articles reviewed in the table defined the project settings (single or multi-center).
Abbreviations: AUC, area under the curve; BMI, body mass index; BTPP, black tea polymerized polyphenol; COMP, Cartilage Oligomeric Matrix Protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DNA, deoxyribo nucleic acid; EGCG, Epigallocatechin-3-gallate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MetS, metabolic syndrome; mKOOS, modified-Knee Injury and Osteoarthritis Outcomes Score; mWOMAC, modified-Western Ontario and McMaster Universities Arthritis Index; NAFLD, non-alcoholic fatty liver disease; PAI-1, plasminogen activator inhibitor-1; RCT, randomized-control trial; ROM, range of motion; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; VAS, Visual Analog Scale.

hemoglobin (HbA1c) and a decrease of blood or plasma glucose concentrations. Additionally, 19 of the 36 studies highlighted a decline in serum concentrations of low-density (LDL) and high-density lipoproteins (HDL), and total cholesterol (TC) post-intervention. One investigation examined the ramifications of plant-based supplementation on DNA methylation patterns. Research by Crescenti et al underscored that cocoa intake considerably curtailed DNA methylation levels, elucidating the causal relationship between DNA methylation perturbations and the onset of cardiovascular diseases and their associated risk factors.[40]

Given the extensive data provided, several key points can be elucidated regarding the various plant and herbal preparations and their mechanism on metabolic disorders. Numerous scientific investigations have underscored the potential of plants in decelerating the advancement of metabolic disorders. Extensive studies suggest a linear association between increased intake of plant-derived foods and reduction of susceptibility to chronic conditions.

Berries, black tea, cocoa, and olive are among plants that exert beneficial effects on metabolic markers. For example, Basu et al found a significant improvement in insulin resistance, lowering LDL-C, and decreased serum PAI-1 in obese adults after 14 weeks of high-dose strawberry consumption.[15] Acute strawberry consumption is also reported to significantly elevate the serum concentrations of vitamin C and folate and prolong the LDL oxidation lag time, suggesting the antioxidant potential of strawberries for CVD prevention.[48] Consumption of cherry juice is reported to significantly lower oxidized LDL levels in patients with metabolic syndrome.[19] Likewise, Franck et al found a significant reduction in post-prandial glucose, TG level, systolic blood pressure, and inflammatory markers (IL-6 and TNF-alpha) after eight weeks of supplementation of raspberry.[20] Plants like *Boswellia serrata* and *Camellia sinensis* are reported to improve insulin sensitivity, potentially providing therapeutic options for diabetes management.[33,43,51] Several extracts, including those from *Citrus bergamia* and *Coffea arabica*, are instrumental in modulating lipid profiles by inhibiting key enzymes involved in cholesterol and triglyceride synthesis.[26,50]

Among 36 studies, two studies observed the effect of olive oil supplementation on metabolic biomarkers and ALT enzymes. The study conducted by Shidfar et al observed that a 12-week intake of extra virgin olive oil led to a marked reduction in ALT enzyme levels in individuals with NAFLD ($P = 0.004$). Conversely, the severity of liver steatosis remained relatively stable throughout the study duration.[41] Similar favorable results are also reported in the study conducted by Sanchez et al although no significant differences were found among the study group, olive oil supplementation on endothelial function confers beneficial effects biomarker both in vivo and ex vivo studies.[1]

Interestingly, while the majority of the studies report improvements in the clinical parameters observed during the intervention using plant-based preparations, two studies that observed the effect of coffee supplementation on metabolic and cardio markers reported similar no significant effect. Studies indicate that the intake of coffee or products derived from cocoa did not elicit notable alterations in cardiometabolic biomarkers. Moreover, within coffee formulations, neither chlorogenic acid nor caffeine showcased enhanced efficacy over placebo in mitigating hepatic lipid accumulation, liver stiffness, or other related hepatic parameters in individuals diagnosed with diabetes and NAFLD.[28,44]

Additionally, studies included in this review also observed the effects of herbal preparations as herbal medicine on metabolic disorders. An herbal medicine comprising *Radix Ginseng*, Poria, Rhizoma *Atractylodis macrocephalae*, Semen *Lablab album*, Rhizoma Dioscoreae, Embryo Nelumbinis, Radix Platycodonis, Semen Coicis, Fructus Amomi, Fructus Jujubae, and Radix Glycyrrhizae has been documented to enhance hypoglycemic response and β-cell functionality in overweight or obese individuals presenting with suboptimally managed T2DM. This compound is posited as a compatible adjunctive therapy for oral hypoglycemic agents, offering advantages in weight regulation and lipid metabolism.[31] In a separate study by Khalili et al, herbal formulation encompassing seeds of *Silybum marianum* (L) Gaertn (milk thistle), leaves of *Urtica dioica* L (nettle), and *Boswellia serrata* (olibanum gum) demonstrated marked reductions in serum fasting glucose, HbA1c, and triglyceride concentrations in patients diagnosed with type II diabetes mellitus.[34]

Terminalia chebula is one of the herbal medicines that has been studied clinically both in its single preparation and in combination with other medicinal plants. Dietary supplementation of *Terminalia chebula* in healthy overweight patients has significantly improved joint mobility, comfort, and functional capacity.[47] Furthermore, its combination with *Commiphora mukul* and *Commiphora myrrha* in an herbal formulation is reported to reduce fasting blood glucose, total cholesterol, and low-density lipoprotein cholesterol levels. Shokoohi et al proposed that *T. chebula* inhibits α-glucosidase, and *C. myrrha* reduces the rate of gluconeogenesis in hepatocytes.[33]

Supplementation with bitter gourd (*Momordica charantia*) has demonstrated efficacy in reducing elevated levels of fasting plasma glucose among individuals with prediabetes. Various extracts and constituents of *M. charantia* are postulated to contribute to its glucose-lowering properties through diverse physiological, pharmacological, and biochemical mechanisms. Specifically, the antihyperglycemic action of bitter gourd can be attributed to three primary pathways: reduction of glucose absorption in the intestine, enhancement of insulin secretion, and facilitation of glucose uptake in peripheral tissues.[32] In a prior review, Joseph et al outlined multiple potential mechanisms underlying the hypoglycemic effects of *M. charantia* and its derivatives, including its direct glucose-lowering impact, stimulation of glucose utilization in peripheral and skeletal muscles, inhibition of intestinal glucose absorption, suppression of crucial enzymes involved in gluconeogenesis, activation of key enzymes in the hexose monophosphate pathway, and the preservation of islet β-cell functionality.[52]

Various benefits have been reported to suggest that the intake of plant-based diets or supplementation of herbal preparations could prevent the development of chronic diseases. A primary rationale is that plants encompass an extensive array of components advantageous to health, including vitamins, minerals, and phytochemicals.[53–56] Phytochemical constituents, including chlorogenic acid, caffeine, cafestol, trigonelline, quercetin-3-O-rhamnoside (quercitrin), diosgenin, α-linolenic acid (ALA), anthocyanins, epicatechin, β-carotene, and quercetin, have been recognized for their multifaceted capacities in mitigating inflammation, anti-oxidative stress, and attenuating metabolic syndrome manifestations, attributed to their regulatory effects on biological and physiological processes.[57,58]

Polyphenols are the most reported phytoconstituents that attenuate metabolic disorders by various mechanisms. Berries such as raspberry and strawberry, coffee, prune, and tea are among the plants which rich in polyphenols. Nilsson et al suggest that polyphenols (anthocyanins and flavonols) from berries are attributed to the beneficial effects on CVD and T2DM.[45] Moreover, research indicates that polyphenols may acutely modulate hemodynamic and vascular responses.[19] Cocoa-derived polyphenols have been observed to decrease global DNA methylation, a change mediated by the regulation of pivotal genes central to this epigenetic mechanism.[40] Storniolo et al demonstrated that polyphenols confer protection against endothelial dysfunction induced by elevated glucose and free fatty acid levels, potentially via the modulation of nitric oxide and endothelin-1.[59]

Polyphenol derivative compounds such as picceatanol, oleorepin, chlorogenic acid (CGA), curcumin, resveratrol, epigallocatechin-3-gallate (EGCG), and quercetin have been clinically reported for their beneficial effects in alleviating metabolic disorders. Piceatannol, a stilbene, major polyphenol derivative compound from *Passiflora edulis,* is reported to promote glucose uptake, AMPK phosphorylation, and glucose transporter 4 (GLUT4) translocation, inhibition of intestinal α-glucosidase.[50] Chlorogenic acid (CGA), a predominant polyphenol in coffee, is instrumental in regulating glucose intolerance and hyperlipidemia. In rat liver microsomes, CGAs specifically competitively inhibit glucose-6-phosphate translocase. Additionally, at the cellular level, they activate adenosine monophosphate-activated protein kinase, which subsequently modulates blood glucose homeostasis and suppresses lipid biosynthesis.[60]

Epigallocatechin-3-gallate, epicatechin-3-gallate, and other related polyphenol derivatives have been demonstrated to augment insulin secretion through the enhancement of GLP1 levels.[61] In a clinical study conducted by Morais et al, it was elucidated that EGCG's role in mitigating insulin resistance and liver TG concentrations is linked to diminished lipid uptake and a decrease in inflammatory cytokine levels.[46]

Flavonoids, notably anthocyanins, belong to an extensive group of phenolic compounds that possess antioxidant, anticancer, antimicrobial, cytotoxic, and antimutagenic properties. Anthocyanins influence the nitric oxide biosynthetic trajectory and exhibit inhibitory properties against angiotensin-converting enzyme (ACE).[62] Moreover, anthocyanin-mediated AMPK activation promotes an upsurge in GLUT4 transporters and glucose assimilation while concurrently suppressing gluconeogenesis. Within hepatic lipid metabolic pathways, AMPK modulates the transcriptional levels of PPAR-α, acyl-coenzyme A (acyl-CoA) oxidase, and carnitine palmitoyltransferase-1A.[15,48,63] Clinical investigations have ascertained that strawberries, rich in anthocyanins, can impede glucose translocation from the intestines to the plasma, particularly through the inhibition of the sodium-glucose co-transporter 1 (SGLT1) and the glucose transporter GLUT2.[48]

Other polyphenol derivatives such as flavanones and flavonols are also reported for their beneficial effects. Flavanones such as naringin, neohesperidin, neoeriocitrin, and brutieridin, major phytoconstituents from citrus species

regulate lipid metabolic processes through the inhibition of hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and acyl-CoA cholesterol acyltransferase (ACAT) enzymatic activities. Concurrently, they augment AMPK activity, thereby enhancing glucose assimilation in both muscular and hepatic tissues.[17] Quercetin, bioactive compounds in mulberry, *Terminalia chebula, Trigonella foenum-graecum, and Prunus cerasus* have been identified to mediate several cellular mechanisms. These include the activation of PPAR-α and PPAR-γ, inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells, and upregulation of anti-inflammatory cytokine expression.[38]

It is also interesting to note that major phytoconstituents such as charantin, a typical cucurbitane-type triterpenoid in *M. charantia*, exhibit notable anti-diabetic attributes. Comparative studies indicate that this compound surpasses the efficacy of the oral hypoglycemic drug, tolbutamide.[52] Pterocarpan and kaempferol glycosides from soya (*Glycine max*) are reported to ameliorate insulin sensitivity and improve the plasma glucose levels in high-fat diet (HFD)-induced type 2 diabetic mice.[16,64] Furthermore, compounds such as cinnamyl isobutyrate from *Cinnamomum cassia* and berberine from *Rhizoma coptidis* contribute to glucose homeostasis through various mechanisms, including AMP-activated protein kinase (AMPK) activation.

The Underlying Mechanism of Bioactive Compounds Affecting the Metabolic and Immune System

The relationship between the immune system and metabolic disorders is intricate and multifaceted and increasingly recognized as critical to understanding conditions like obesity, diabetes, and cardiovascular diseases. Modulating the immune system in patients with metabolic disorders can offer several potential benefits including reducing chronic low-grade inflammation, enhancing insulin sensitivity as the immune system plays a role in the development of insulin resistance, and influencing the gut microbiota creating a more balanced metabolic environment.[65]

Table 2 elucidates a compelling cross-section of plant-based interventions that exert both metabolic and immunomodulatory effects, substantiated by specific bioactive constituents and corresponding mechanisms of action. These plants' dual roles suggest a complex interplay between metabolic and immune systems, potentially mediated by a range of molecular targets, including but not limited to cytokines, lipid metabolism pathways, and glucose transport mechanisms.

Among thirty-six studies, thirty-eight plants are employed either in their single preparations, combination or enriched with other phytoconstituents to enhance their pharmacological effect. Several plant-based supplementation or herbal preparations containing key phytoconstituents are reported to exhibit beneficial effects not only for various metabolic diseases but also on the immune system. Bioactive compounds are often associated with diverse potentials possessing a multifaceted capacity to manifest anti-inflammatory, antioxidative, and anti-metabolic syndrome effects; these agents adeptly regulate both biological and physiological processes.[57,58]

Interestingly, the majority of plants that work on metabolic disorders were reported to activate the immune system. Alterations in metabolic responses are linked to numerous immunological signaling pathways, for example, metabolic hormones (leptin, resistin, and adiponectin) play various roles in immunological functions.[92] Plants such as *Boswellia serrata, Cinnamomum cassia, Citrus bergamia, Coffea arabica, Ficus racemosa, Momordica charantia, Morus Alba, Trigonella foenum graecum*, and many others (depicted in Figure 2) affect multiple biochemical pathways, displaying not just metabolic but also immunological benefits. *Boswellia serrata, Camellia sinensis*, and *Citrus bergamia* are reported to not only improve insulin sensitivity but also reduce the levels of pro-inflammatory cytokines such as IL-6 and TNF-α and positively modulate T lymphocyte proliferation and natural killer (NK) cell function.[65,68,90]

The multifaceted impact of phytoconstituents on various physiological processes suggests a complex network of interactions. Consequently, attributing the potential metabolic benefits of phytoconstituents to a singular component or attribute appears challenging. Instead, phytoconstituents may exert their effects through a range of mechanisms, such as improved glucose regulation, reduced inflammatory responses, and immune system modulation. Trigonelline in fenugreek seeds helps improve diabetes through several mechanisms, such as regulating insulin release, decreasing oxidative stress, and enhancing both glucose tolerance and insulin sensitivity. Additionally, it has been documented that there is an augmentation in the phagocytic index and antibody titer. Additionally, there is modulation of the expression of pro-

Table 2 Mechanism of Action of Plants on Metabolic Disorders and Immune System

Plants/Herbal/ Vegetable Preparation*	Family	Major/Active Constituents	Mechanisms on Metabolic Disorders	Immunomodulatory Activity
Boswellia serrata	*Burseraceae*	Olibanum, an aromatic resin	• Augmentation of insulin sensitivity and protecting pancreatic β-cells[34]	• COVID-19 patients demonstrated an elevated lymphocyte count accompanied by a decline in C-reactive protein (CRP), lactate dehydrogenase (LDH), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) concentrations.[66]
Camellia sinensis	*Theaceae*	EGCG	• EGCG decreased lipid uptake and the abatement of inflammatory cytokine concentrations[46,67]	• Extracts stimulated cytokine production, T lymphocyte proliferation, and reportedly augmented lymphocytes, monocytes, IL-1α, and IL-1β production[68]
Cinnamomum cassia	*Lauraceae*	Cinnamyl isobutyrate	• Inhibition of α-glucosidase and pancreatic α-amylase, modulation of glucose synthesis through the alteration of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) pathways, and modulation of cholesterol and fatty acid uptake via deactivation of Niemann-Pick C1-like 1 and Cd36 mRNA receptors, paired with a concurrent decrease in chylomicron synthesis[36]	• Volatile oils from *Cinnamomum cassia* twig, derived from eight selected herbs, robustly enhanced IL-1β and IL-6 release from ANA-1 murine macrophage[69]
Citrullus lanatus	*Cucurbitaceae*	Citrulline, lycopene, and β-carotene[26]	• Citrulline and its enriched form in watermelon juice amplify the circulating arginine reservoir and intensify the NO synthase activation more robustly than arginine alone[26]	• Phytol arrests the growth of the human T-cell leukemia Jurkat cell line and impedes tumor progression in an A549 human epithelial cell xenograft mouse model. This is associated with S-phase cell cycle arrest and downregulation of specific cyclins and signaling pathways.[70]
Citrus Bergamia	*Rutaceae*	Naringin, neohesperidin, neoeriocitrin, brutieridin, and melitidin Bergapten and bergamottin	• Lipid metabolic pathways are modulated by inhibiting hepatic 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase and acyl-CoA cholesterol acyltransferase (ACAT); concurrently, there is an elevation in AMPK activity and enhancement in glucose uptake in skeletal muscles and hepatic tissues[39]	• Gene expression modulation related to chemotaxis, adhesion, and cell infiltration was observed, along with decreased plasma concentrations of inflammatory markers in non-diabetic subjects[71]

Coffea arabica	*Rubiaceae*	Chlorogenic acid (CGA), caffeine, cafestol, trigonelline, and melanoidin	• Regulation of glucose intolerance and amelioration of hyperlipidemia[28] • At both microsomal and cellular levels, there's an impediment of the glucose-6-phosphate translocase and activation of the adenosine monophosphate-activated protein kinase, subsequently leading to the maintenance of blood glucose stability and reduction in lipid biosynthesis[28]	• Notable suppression of inflammatory cytokines, reduced macrophage migration, and enhanced immunological signaling were observed. • Expansion of oxidative processes was effectively halted.[72]
Curcuma Zedoaria Roscoe	*Zingiberaceae*	Zederone, curzerenone, 1,3–hydroxygermacrone, epicurzerenone, curcumol, zedoarol, curcolone, ar–turmerone, zedoarondiol, isocurcumenol, furanodiene, curdione, curcumenol, curcumanolide A, and zingiberene	• Curcumin demonstrates efficacy in decreasing serum cholesterol, preventing LDL oxidation, inhibiting platelet aggregation, and suppressing thrombotic events	• Curcumin attenuated the activation of the NF-κB signaling cascade, concurrent with NLRP3 silencing through siRNA transfection[73]
Ficus racemosa	*Moraceae*	Glycosides, β-sitosterol and lupeol	• β-sitosterol serves as a cholesterol-lowering agent through its mechanism of impeding cholesterol absorption in the gastrointestinal tract[30]	• Compounds isolated from *Ficus racemosa* exhibited pronounced cell migration augmentation in specific cell lines[74]
Glycine max	*Fabaceae*	Soybean contains isoflavones (daidzin, genistin, and malonyl genistin), while soy leaves contain pterocarpan and kaempferol glycosides	• A kaempferol glycoside-rich fraction derived from unripe soybean foliage has shown to diminish blood glucose and hepatic lipid concentrations in KK-Ay murine models[75] • Pterocarpan has shown promising results in improving insulin sensitivity and regulating plasma glucose concentrations in high-fat diet-induced type 2 diabetic mice[64]	• Soy isoflavones and their metabolites modulated natural killer (NK) cell activity. Genistein specifically attenuated IL-12/IL-18-induced interferon-gamma (IFN-γ) production compared to controls[76]
Juglans sp.	*Jugalanaceae*	Λ-linolenic acid (ALA), a plant-based omega-3 fatty acid, hydrolyzable tannins[77]	• Alpha-lipoic acid exhibits its cardio-protection through myriad pathways, inclusive of attenuating plaque mineralization, lipid profile optimization, endothelial function maintenance, and demonstrating anti-thrombotic, anti-arrhythmic, and anti-inflammatory actions.[37]	• Walnut consumption may enhance the proliferation of beneficial bacterial species in the gut, indirectly influencing immune system functionality.[77]
Lycopersicon esculentum L.	*Solanaceae*	Carotenoids (mainly lycopene and β-carotene), phenolic compounds (mainly flavonoids, such as naringenin), vitamins C and E, potassium and folates	• Lycopene manifests various salutary effects, including LDL-C reduction, inflammation marker suppression, blood pressure moderation, and enhancement of flow-mediated dilation[53,78]	• Gamma-aminobutyric acid (GABA) derived from tomatoes demonstrated similarities with biologic GABA found on peripheral immune system cells[79]

(*Continued*)

Table 2 (Continued).

Plants/Herbal/ Vegetable Preparation*	Family	Major/Active Constituents	Mechanisms on Metabolic Disorders	Immunomodulatory Activity
Momordica charantia	*Cucurbitaceae*	Peptides that resemble insulin (P-insulin), charantins, momordicosides, oleanic acid, trehalose, and momordin	• Decreasing intestinal glucose absorption, enhancing insulin release, and promoting glucose uptake in peripheral cells[32]	• Polysaccharides were found to bolster specific immune markers in mice with cyclophosphamide-induced immunosuppression[80]
Morus alba	*Moraceae*	Flavonols including rutin, morin, quercetin, and myricetin	• Quercetin is involved in the activation of PPAR-α and PPAR-γ, impediment of nuclear factor kappa-light-chain-enhancer activation in B cells, and upregulation of anti-inflammatory cytokine expression[38]	• Ratios between specific T helper cell populations and cytokine secretion profiles were altered[63]
Olea europaea	*Oleaceae*	Monounsaturated fatty acids (MUFAs), polyphenols, and triterpenes, Oleuropein	• Polyphenols exhibit protective qualities against endothelial dysfunction triggered by elevated glucose and free fatty acids by modulating nitric oxide and endothelin-1 ratios[59]	• Downregulation of genes integral to inflammation, lipid metabolism, and oncogenesis was observed.[41]
Panax ginseng	*Araliaceae*	Ginsenosides, polysaccharides, steroids, and flavonoids	• Ginsenosides play a dual role in reducing gluconeogenesis and facilitating glucose transport and insulin biosynthesis; they also modulate cellular redox equilibriums or histone acetylation via SIRT1 and NRF2 activations and their downstream gene expressions[81]	• Ginsenoside-Rb1 potentially inhibited TNF-α formulation in LPS-stimulated RAW264.7 macrophages[82]
Passiflora edulis	*Passifloraceae*	Piceatannol	• Conspicuous reductions in blood glucose levels were recorded in mice on high-fat diets or db/db mouse models, without discernible changes in body weight or visceral adiposity • The activation of SIRT1 and AMPK pathways suggest an improved metabolic state[83]	• Piceatannol significantly modulated VEGF-induced cellular activities and vascular formation in zebrafish embryos, likely through VEGF signaling interference.[84]
Prunus cerasus	*Rosaceae*	Anthocyanins, including cyanidin 3-glucosylrutinoside, cyanidin 3-rutinoside, cyanidin sophoroside, and peonidin 3-glucoside; flavonols, including isorhamnetin rutinoside, kaempferol, and quercetin; flavonols, including catechin, epicatechin, and procyanidins B1 and B2	• In hyperglycemic mouse models, the suppression of pro-inflammatory cytokines indicates potential therapeutic interventions for degenerative diseases or diseases linked with cell activation[19]	• Reduction in pro-inflammatory molecule production was documented.[85]

Rhizoma coptidis	*Ranunculaceae*	Berberine	• The role of AMP-activated protein kinase (AMPK) as an activator is multifaceted, ranging from inducing glucose transporter-4 and insulin receptor mRNA expressions to being an α-glucosidase inhibitor, a glucagon-like peptide-1 (GLP-1) inducer, and an inhibitor of mitochondrial respiratory chain complex I, cumulatively stimulating glycolysis[31]	• Infections resulted in attenuated serum interferon-gamma and intestinal TNF-α concentrations.[86]
Silybum marianum (L)	*Asteraceae*	Flavonolignans (70–80%) containing silymarin, silibinin, silydianin, and silychristin	• The influence on pancreatic β-cell functionality and the insulin secretagogue effect is both regulatory and protective[34]	• The NF-κB signaling pathway and TNF-α activation were suppressed, with variances in T-lymphocyte functionality based on dosage.[87]
Smallanthus sonchifolius Poepp	*Asteraceae*	Fructooligosaccharides (FOS) and phenolic compounds content, mainly chlorogenic acid	• Fructooligosaccharides and their fermentation by-products impact gut flora, especially focusing on Lactobacillus and Bifidobacterium species, engendering a healthier gut microenvironment[14]	• Fructooligosaccharides (FOS) derived from Yacon manifested non-specific immunomodulatory effects against heat-inactivated yeast.[88]
Terminalia chebula	*Combretaceae*	Tannins include gallic acid, ellagic acid, chebulic acid, chebulinic acid, punicalagin, and tannic acid; flavonoids include quercetin, catechin, and kaempferol; Saccharides include D-glucose, D-fructose, and saccharose; fruit acids include quinic acid and shikimic acid	• Hydrolyzable tannins, including chebulagic acid, chebulinic acid, and gallic acid, have been characterized for their anti-inflammatory and antioxidant properties. Evaluations using experimental arthritis pain models and in vitro methodologies have highlighted their potential to inhibit TNF-alpha, IL-6, NF-kappaB, nitric oxide radical scavenging, and T-cell-mediated cytotoxic responses which involves promoting phosphorylation of insulin receptors, enhancing insulin-driven glucose transportation, and inhibiting genes vital for adipogenesis, tilting the balance towards glucose metabolism[47]	• Specific acids displayed antioxidant properties, possibly contributing to their immunomodulatory activities, with observed changes in antioxidant enzymes and specific immune cells. • Elevations in pineal gland melatonin concentrations and specific cytokines were noted, with potential implications for immune function.[89]
Trigonella foenum-graecum	*Fabaceae*	Seeds contain alkaloid trigonelline, steroidal saponins, galactomannan, quercetin-3-O-rhamnoside (quercitrin), saponins including diosgenin	• Fibrous components slow down gastric emptying, which in turn moderates post-prandial blood glucose elevations. Trigonelline may contribute to reduced glycosuria • Diosgenin acts as a barrier to cholesterol absorption, resulting in decreased hepatic cholesterol concentrations[90]	• Immune modulation in macrophage cells and altered CD4+ and CD8+ counts in diabetic mice were observed, potentially linked to NF-κB activity[90]
Urtica dioica L	*Urticaceae*	Neophytadiene, phthalic acid, dibutyl phthalate, bis (2-ethyl hexyl) maleate, and 1.2-benzenoid carboxylic acid	• Insulin secretagogue activity, mimicking insulin functions, exhibiting PPAR (peroxisome proliferator-activated receptor)-γ agonistic behavior, and inhibiting α-glucosidase functions[91]	• Compounds showcased antioxidant properties without displaying cytotoxicity to macrophages and hepatocytes at active concentrations[91]

Notes: *Only major components of the poly-herbal preparations are listed in the table.

Plants with bioactive metabolites

Alleviating metabolic disorders

T2DM and NAFLD
- *Adansonia digitata*
- *Boswellia serata*
- *Camelia sinensis*
- *Cinnamomum cassia*
- *Citrus bergamia*
- *Coffea arabica*
- *Comiphora mukul*
- *Comiphora myrrha*
- *Ficus racemosa*
- *Momordica charantia*
- *Morus alba*
- *Panax ginseng*
- *Rhizoma coptidis*
- *Scoparia dulcis*
- *Silybum marianum*
- *Terminalia chebula*
- *Trigonella foenum-graecum*
- *Urtica dioca*

Hyperlipidemia and Obesity
- *Camelia sinensis*
- *Cinnamomum cassia*
- *Citrulus lanatus*
- *Curcuma Zedoaria Roscoe*
- *Fragaria × ananassa*
- *Olea europaea*
- *Prunus domestica*
- *Smallanthus sonchifolius Poepp*
- *Terminalia chebula*

Cardiovascular disorders and MetS
- Cocoa
- *Coffea arabica*
- *Fragaria × ananassa*
- *Glycine max*
- *Juglans sp.*
- *Lycopersicon esculentum L*
- *Olea europea*
- *Passiflora edulis*
- *Prunus cerasus*
- *Rubus ideaus L.*

Activating immune system

Pro-inflammation
- *Boswellia serata*
- *Cinnamomum cassia*
- *Citrus bergamia*
- *Coffea arabica*
- *Curcuma Zedoaria Roscoe*
- *Glycine max*
- *Momordica charantia*
- *Morus alba*
- *Panax ginseng*
- *Passiflora edulis*
- *Prunus cerasus*
- *Rhizoma coptidis*
- *Silybum marianum*
- *Trigonella foenum-graecum*

Antioxidant and enhance macrophage activity
- *Camelia sinensis*
- *Ficus racemosa*
- *Fragaria × ananassa*
- *Lycopersicon esculentum L*
- *Olea europaea*
- *Panax ginseng*
- *Smallanthus sonchifolius Poepp*
- *Terminalia chebula*
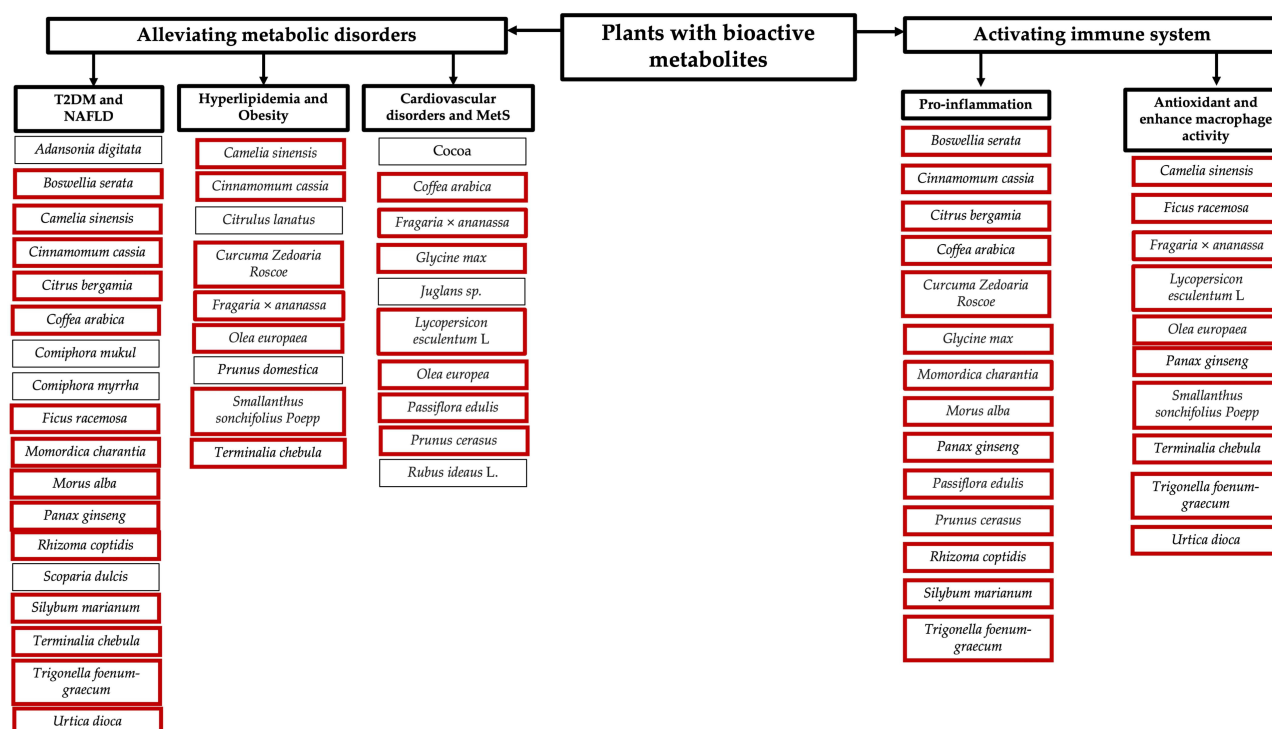- *Trigonella foenum-graecum*
- *Urtica dioca*

Figure 2 Plants that alleviate metabolic disorders and activate the immune system. The thin black outline denotes the plants that have been reported clinically solely for their activity in metabolic disorder and their mechanisms in immune system have not been reported in details. While the boxes with a red outline signify that the plants are reported not only for their benefit in metabolic disorders clinically but also affect multiple biochemical pathways in immune system.

inflammatory and M1/M2 immunoregulatory markers within THP-1 macrophage cells mediated by NF-κB activity. Concurrently, an increase in CD4+ and CD8+ values has been observed in diabetic mice.[29,90]

Furthermore, polyphenols are bioactive compounds that attenuate metabolic disorders by various mechanisms. Polyphenolic compounds, including epigallocatechin-3-gallate, epicatechin-3-gallate, and epigallocatechin, have been demonstrated to augment insulin secretion via an elevation in GLP-1 levels.[61] Notably, epigallocatechin-3-gallate (EGCG) has exhibited the potential to ameliorate autoimmune disease symptoms in animal models. Mice administered with EGCG showed a significant increase in Treg cells within the lymph nodes and spleen, coupled with an attenuated T-cell response. Furthermore, a clinical investigation by Morais et al elucidated that EGCG's role in mitigating insulin resistance and hepatic TG concentrations can be ascribed to its effect in decreased lipid uptake and lowering pro-inflammatory cytokine levels.[46] EGCG was also claimed to modulate the immune system through the modulation of cytokine production and T lymphocyte proliferation, as well as its enhancement of lymphocyte, monocyte, IL-1α, and IL-1β production.[51]

Isoflavones and their metabolites from soy influence the signaling and functional mechanisms of natural killer (NK) cells. Specifically, genistein attenuates the production of interferon-gamma (IFN-γ) induced by interleukin (IL)-12/IL-18 compared to control groups. Comprehensive cellular studies reveal that genistein mitigates IFN-γ production triggered by IL-12/IL-18 in human NK cell subsets without consistently affecting their cytotoxic capabilities. In terms of intracellular signaling, genistein reduces both the total tyrosine phosphorylation and the phosphorylated components of the MAPK pathway elicited by IL-12/IL-18 stimulation.[76]

Conclusion

This review reveals potential synergistic effects in which the same plants that improve metabolic markers also enhance immune response modulation. The comprehensive analysis of thirty-six studies investigating the impact of plant-based diets and phytochemicals on metabolic disorders substantiates the significant role of plant-based diet interventions in

mitigating various conditions related to metabolic disorders. The evidence indicates that plant-based foods with an abundant content of phytochemicals confer notable improvements in glycemic control, lipid profiles, weight management, blood pressure, and inflammatory markers. Furthermore, numerous studies demonstrate that phytochemicals from a diverse range of plants and herbal preparations exert multifunctional therapeutic effects which have been associated with improved insulin resistance, reduced LDL-cholesterol, decreased levels of inflammatory markers, and enhanced insulin sensitivity, offering promising avenues for the management of DM and CVD. Additionally, the correlation between the immune system and metabolic disorders is increasingly recognized, with corroborations suggesting that plant-based interventions can exert immunomodulatory effects. Plants such as *Boswellia serrata, Cinnamomum cassia, Citrus bergamia, Coffea arabica, Ficus racemosa, Momordica charantia, Morus alba, Trigonella foenum graecum*, and many others, could affect multiple biochemical pathways which correspond to the relationship between metabolic health and immune function.

Acknowledgments

Disclosure

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