



Phytochemicals in the Management of Metabolic Disorders: Molecular Mechanisms and Pharmacological Evidence

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Article History:

Received : 2025-12-22

Revised : 2026-02-28

Accepted : 2026-04-10

Published : 2026-04-26

Abstract

Metabolic disorders, including obesity, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease, are driven by interconnected disturbances in insulin signalling, lipid metabolism, oxidative stress, inflammation, mitochondrial function, and energy homeostasis. Despite extensive experimental evidence supporting phytochemicals as multi-target metabolic modulators, their clinical translation remains limited by variable bioavailability, inconsistent formulations, heterogeneous dosing, and insufficient high-quality human studies. This review aims to synthesise current mechanistic, pharmacological, and clinical evidence on major phytochemical classes and their therapeutic relevance across common metabolic disorders. The review integrates evidence on polyphenols, flavonoids, anthocyanins, curcuminoids, phytosterols, terpenoids, alkaloids, and related plant-derived compounds from dietary and medicinal sources. Available findings indicate that phytochemicals can modulate AMP-activated protein kinase, PI3K/Akt, Nrf2, NF- κ B, peroxisome proliferator-activated receptors, autophagy, mitophagy, adipokine signalling, and epigenetic regulation, thereby improving glucose utilisation, insulin sensitivity, lipid handling, redox balance, and inflammatory control. Their potential extends across diabetes, obesity, dyslipidemia, metabolic syndrome, hepatic steatosis, and associated skeletal muscle dysfunction. Preclinical evidence is generally consistent, whereas clinical findings remain heterogeneous. Phytochemicals represent promising adjunctive candidates for metabolic disease management, but reliable clinical integration will require standardised preparations, pharmacokinetic optimisation, rigorous safety assessment, and adequately powered randomized trials with clinically meaningful endpoints.

Keywords: Metabolic disorders, Molecular mechanisms, Phytochemicals, Polyphenols, Therapeutic potential

1. Introduction

Metabolic disorders are a significant and growing public health issue as they involve complex interrelated disorders that have a negative impact on glucose metabolism, lipid metabolism, cardiovascular health, and overall metabolic health (Halagali et al., 2025). Obesity, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease are all important elements of this spectrum that often are associated with each other by common metabolic abnormalities (Dama et al., 2024). As these diseases become more common, the need for early and/or therapeutic interventions to address multiple pathogenic mechanisms instead of individual metabolic aberrations has grown (Hossain et al., 2025).

Insulin resistance is a common denominator to multiple metabolic disorders, and it leads to decreased insulin action, increased insulin secretion, abnormal lipid metabolism, and progressive metabolic defects (Ansari et al., 2023). Chronic low-grade inflammation also facilitates inflammatory signalling that disrupts insulin responses and alters cellular metabolic reactions, which is another factor that affects metabolic deterioration (Zamani-Garmsiri et al., 2022). Oxidative stress is also implicated in the progression of metabolic disease due to the detrimental effects of excess ROS on cell structure, function, and the activation of inflammatory pathways (Dama et al., 2024). Mitochondrial dysfunction has also been identified as a significant pathogenic mechanism, especially if the impairment of mitochondrial quality control can impair energy metabolism and lead to metabolic tissue injury (Su et al., 2021). Abnormal cholesterol and lipoprotein metabolism is another factor that exacerbates the cardiometabolic risk associated with increased LDL cholesterol levels and associated vascular complications (Islam et al., 2021).

The interrelationships of these mechanisms have increased interest in the use of phytochemicals as multi-target agents in the management of metabolic disease (Rodríguez-Negrete et al., 2024). Fruits and vegetables, grains, medicinal plants, herbs, and dietary-derived plants contain naturally occurring bioactive compounds called phytochemicals, which may promote and regulate cellular and molecular processes that are important to human health (Hossain et al., 2025). The polyphenols, flavonoids, phenolic acids, phytosterols, carotenoids, terpenoids, and other secondary metabolites from plants with various pharmacological properties are major constituents (Gasmi et al., 2022). The antioxidant and anti-inflammatory properties of polyphenols, as well as their potential to affect metabolic signalling pathways linked to insulin resistance and chronic inflammation have drawn special interest (Zamani-Garmsiri et al., 2022). Experimental and clinical studies have revealed the effects of flavonoids on glucose and lipid metabolism, oxidative stress, inflammation and related molecular signalling pathways (Yi et al., 2021). The citrus flavonoids have also been found to exhibit anti-diabetic effects in relation to glycemic control, insulin signaling, oxidative stress, inflammation, and diabetes associated complications, etc. (Gandhi et al., 2020).

Medicinal plants and plant-based foods are hence a pharmacologically diverse source of compounds that have potential in preventing and managing metabolic abnormalities (Nyakudya et al., 2020). They are made even more relevant by the fact that individual phytochemicals have been found to have multiple effects on oxidative stress, inflammatory signalling, mitochondrial function, glucose homeostasis, and lipid metabolism (Su et al., 2021). While conventional pharmacological therapies continue to be critical in the management of metabolic disease, the use of multiple agents is often necessary in order to manage interconnected risk factors and complications of metabolic disease over the long term (Halagali et al., 2025). This therapeutic complexity has led to the investigation of phytochemicals as complementary bioactive compounds that can help control metabolism in a more general way through their direct action on other molecules (Rodríguez-Negrete et al., 2024).

Although there is significant experimental evidence, the translation of phytochemicals into clinical routine use is hindered by bioavailability differences, dosage amounts,

formulation, and the level of human clinical evidence (Hossain et al., 2025). There is therefore a need for a critical evaluation that will establish a molecular mechanism correlation with pharmacological and clinical data, which will allow the identification of those phytochemicals that have the greatest therapeutic potential and areas of knowledge gaps.

1.1 Objectives of the review

This review aims to examine the therapeutic potential of phytochemicals in major metabolic disorders by integrating current evidence on their molecular mechanisms and pharmacological effects. It focuses on their influence on insulin resistance, oxidative stress, inflammation, mitochondrial function, glucose homeostasis, and lipid metabolism. It also evaluates available preclinical and clinical evidence, while identifying key limitations related to bioavailability, safety, standardisation, and clinical translation.

2. Review

2.1 Major Classes and Sources of Metabolically Active Phytochemicals

Metabolically active phytochemicals are structurally diverse compounds found in plants that have the ability to influence glucose and lipid metabolism, oxidative stress, inflammation and insulin signalling. One of the most widely studied polyphenols are flavonoids, phenolic acids, stilbenes and other compounds containing polyphenols which are useful for their antioxidant and anti-inflammatory properties associated with metabolic dysfunction (Nainu et al., 2023). One of the largest subgroups of polyphenols is flavonoids, which include several that are active in redox-sensitive and insulin-related signalling pathways, such as quercetin, catechins, and anthocyanins (Qin et al., 2022). Berries, grapes and other pigmented plant foods are rich in anthocyanins, which have been explored for their ability to impact oxidative and inflammatory processes linked to metabolic disease (Nainu et al., 2023). The pharmacological properties of curcuminoids, especially those of curcumin from *Curcuma longa*, are pleiotropic and related to the regulation of glycemic levels, oxidative stress, and inflammatory response (Ansari et al., 2022). Phytosterols, which structurally resemble cholesterol, have been studied for their impact on lipid metabolism, insulin resistance, and associated metabolic issues (Prasad et al., 2022).

Other pharmacological activities of phytochemicals, for example, terpenoids and alkaloids, have also been observed, including those with antihyperglycemic, antioxidant, and anti-inflammatory effects (Ansari et al., 2022). These bioactive components are found in a wide variety of fruits, vegetables, legumes, grains, herbs, spices, and medicinal plants. They are chemically diverse and have multiple metabolic target activities, making them effective therapeutic agents for preventing and managing metabolic disorders and providing further research opportunities (Nainu et al., 2023). The principal molecular actions of phytochemicals are illustrated in Figure 1.

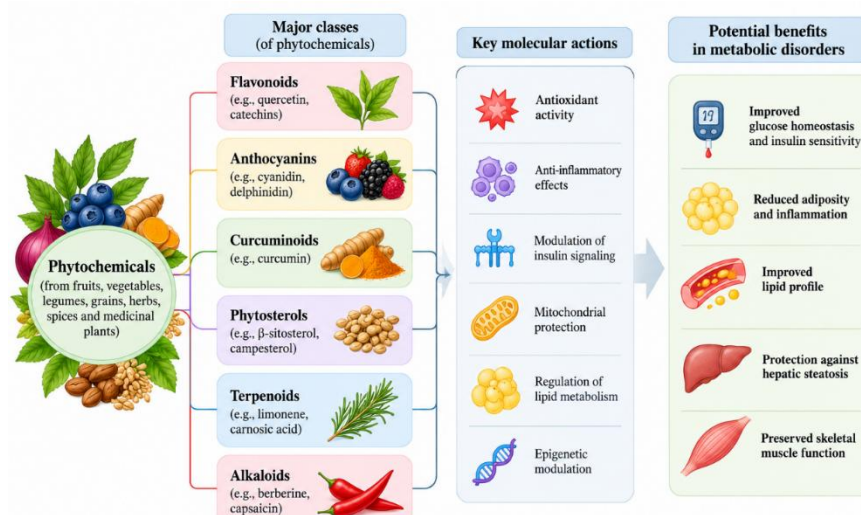


Figure 1: Key molecular mechanisms of phytochemicals in metabolic disorders

2.2 Molecular Mechanisms Underlying the Metabolic Effects of Phytochemicals

The effects of phytochemicals on metabolic homeostasis are linked to the various pathways involved in insulin action, oxidative balance, inflammation, mitochondrial function and lipid metabolism. AMP-activated protein kinase activation is a mechanism of interest since it boosts glucose uptake, enhances fatty acid oxidation, and reduces hepatic lipogenesis and energy-consuming anabolic processes (Martín and Ramos, 2024). Multiple antioxidant phytochemicals have also been shown to be able to modulate the PI3K/Akt pathway, which promotes insulin receptor signalling and glucose uptake in insulin-sensitive tissues (Arabshomali et al., 2023).

Another important pharmacological effect is the control of oxidative stress. The phytochemicals may strengthen the endogenous antioxidant defence in an Nrf2-dependent mechanism by decreasing the injury to cells provoked by reactive oxygen species (ROS) that are believed to play a role in insulin resistance and dysfunction of the pancreatic β -cells (Arabshomali et al., 2023). They have anti-inflammatory effects through NF- κ B signaling inhibition and the resulting decrease in pro-inflammatory mediators that contribute to chronic metabolic inflammation (Arozal et al., 2020). Additionally, the regulation of peroxisome proliferator-activated receptors is another factor that promotes better lipid oxidation, adipocyte function, insulin sensitivity and hepatic lipid handling (Martín & Ramos, 2024).

Anthocyanins are an example of this multi-pathway activity, playing a role in redox regulation, inflammatory signalling, glucose utilization and lipid metabolism (Nistor et al., 2022). Phytochemicals can also impact mitochondrial biogenesis, autophagy, adipokine secretion, and epigenetic regulation, in addition to their activity as multi-target modulators, not single-pathway agents (Martín & Ramos, 2024).

2.3 Phytochemicals in Insulin Resistance and Type 2 Diabetes Mellitus

The interest in phytochemicals and type 2 diabetes mellitus has been significant as they have the potential to target various mechanisms associated with insulin resistance, impaired glucose utilisation, β -cell dysfunction, oxidative stress, and chronic inflammation. Natural bioactive compounds can help control blood glucose levels through the increase of insulin sensitivity, an increase in glucose uptake in the periphery and modulation of pathways that regulate glucose and lipid metabolism (Noce et al., 2021). They are especially relevant in insulin-resistant states, which lead to adverse insulin signalling in skeletal muscle, adipose tissue and liver, resulting in chronic hyperglycemia and impaired metabolic functions (Kumar et al., 2022).

Other phytochemicals also have antioxidant and anti-inflammatory properties that

could help to maintain pancreatic β -cell function and minimise metabolic stress due to diabetes progression (Noce et al., 2021). An additional mechanism is epigenetics, which can be modulated by plant-based compounds, as they can affect DNA methylation, histone modifications and non-coding RNA pathways involved in insulin signaling and glucose metabolism (Ramirez-Alarcon et al., 2021). These activities are consistent with the idea of selected phytochemicals as “epidrugs” that have the potential to modify gene expression levels, without inducing changes in the DNA sequence of the gene (Ramirez-Alarcon et al., 2021).

Epigallocatechin-3-gallate is one of the most well-studied compounds, showing promising properties in relation to oxidative stress, inflammation, glucose metabolism, and insulin signalling pathways (Alam et al., 2024). While the potential for clinical application remains, the findings from these experimental and clinical studies indicate that phytochemicals could supplement existing therapeutic approaches, with individual studies often differing in terms of dose, formulation, bioavailability, and study design (Alam et al., 2024). The major antidiabetic actions of phytochemicals are summarised in Table 1.

Table 1: Key mechanisms of phytochemicals in type 2 diabetes mellitus.

Phytochemical action	Principal molecular/physiological effect	Relevance to T2DM	References
Improvement of insulin sensitivity	Enhances insulin-responsive signaling and peripheral glucose uptake	Helps reduce insulin resistance and improve glycemic control	Noce et al. (2021); Kumar et al. (2022)
Regulation of glucose and lipid metabolism	Modulates pathways controlling glucose utilisation and lipid handling	Supports metabolic homeostasis and may reduce chronic hyperglycemia	Noce et al. (2021); Alam et al. (2024)
β -cell protection	Reduces oxidative and inflammatory stress affecting pancreatic β -cells	May preserve insulin-secretory function during disease progression	Noce et al. (2021); Alam et al. (2024)
Antioxidant and anti-inflammatory activity	Attenuates oxidative stress and chronic inflammatory signalling	Limits metabolic stress associated with insulin resistance and diabetes complications	Noce et al. (2021); Alam et al. (2024)
Epigenetic modulation	Influences DNA methylation, histone modification, and	May modify expression of genes involved	Ramirez-Alarcon et al. (2021); Alam

	non-coding RNA pathways	in insulin signalling and glucose metabolism	et al. (2024)
Epidrug-like activity	Alters metabolically relevant gene expression without changing DNA sequence	Offers a potential mechanism for long-term regulation of metabolic pathways	Ramirez-Alarcon et al. (2021); Noce et al. (2021)
EGCG-mediated metabolic regulation	Modulates oxidative stress, inflammation, glucose metabolism, and insulin signaling	Provides multi-target support for metabolic control in T2DM	Alam et al. (2024); Noce et al. (2021)
Translational considerations	Effects vary with dose, formulation, bioavailability, and study design	Highlights the need for standardized clinical evaluation	Alam et al. (2024); Kumar et al. (2022)

2.4 Phytochemicals in Obesity and Adipose Tissue Dysfunction

Obesity affects not only the accumulation of fat, but also causes adipocyte hypertrophy, changes in the secretion of adipokines, chronic low-grade inflammation, oxidative stress and metabolic signalling. These abnormalities can be influenced by the phytochemicals which can regulate adipogenesis, lipogenesis, lipolysis, fatty acid oxidation and thermogenesis (Li et al., 2022). They are structurally diverse and interact with multiple metabolic targets that regulate adipocyte differentiation and whole-body energy balance, respectively (Li et al., 2022).

Other phytochemicals inhibit the transcription pathways responsible for the maturation of adipocytes and lipid storage, which helps to avoid an excessive accumulation of triglycerides in adipose tissue (Li et al., 2022). Others stimulate fatty acid oxidation and energy expenditure which can lead to a decrease in ectopic lipid deposition and enhance metabolic flexibility (Santa et al., 2023). These impacts are applicable due to the pro-inflammatory effects of adipocytes and the disruption of adipokine signalling (Cote et al., 2022) in adipose tissue.

Oxidative stress is also a mediator of adipose dysfunction, as it contributes to cell injury, inflammatory activation and imbalance in redox-sensitive pathways. The processes may be counteracted by the antioxidant phytochemicals, which decrease the production of ROS and increase the antioxidant capacity of the host organism (Muscolo et al., 2024). Some compounds can also activate thermogenic pathways and induce browning of WAT, leading to higher energy expenditure (Li et al., 2022). These collectively can aid in the further exploration of phytochemicals as co-modulators of excess adiposity and the metabolic dysfunction of obesity (Santa et al., 2023).

2.5 Phytochemicals in Dyslipidemia, Cardiometabolic Risk, and Metabolic Syndrome

Dyslipidaemia and metabolic syndrome are related abnormalities in lipids, insulin sensitivity, liver function and vascular homeostasis that all contribute to a greater

cardiometabolic risk. These abnormalities can be positively regulated by phytochemicals through inhibiting lipid biosynthesis, promoting fatty acid oxidation, and regulating lipid and cholesterol metabolism pathways (Liu et al., 2022). They have been shown to have hypolipidemic properties and have been associated with modulating enzymes and transcriptional factors that regulate hepatic lipogenesis, lipid transport and lipid clearance (Liu et al., 2022).

In metabolic syndrome, several target interventions are especially pertinent because of the concurrent development of insulin resistance, obesity, hypertriglyceridemia and altered cholesterol levels. There are some phytochemical combinations that are suggested to have complementary effects on insulin signaling and lipid handling, and the evidence is inconsistent (David, 2025). These actions could be particularly relevant in those with both diabetes and obesity, where the metabolic abnormalities are likely to synergise.

Curcumin is an example of a compound that has various effects on the cardiometabolic system, including on hepatic lipid accumulation, oxidative stress, inflammatory signaling, and insulin-related pathways (Guariglia et al., 2023). These mechanisms are important in the case of metabolic dysfunction-associated steatotic liver disease, which is often accompanied by dyslipidemia and insulin resistance (Guariglia et al., 2023). Overall, current evidence is supportive of ongoing research on the use of phytochemicals as complementary treatments to treat lipid abnormalities and the cluster of metabolic abnormalities underlying cardiometabolic disease (Liu et al., 2022). The cardiometabolic actions of phytochemicals are illustrated in Figure 2.

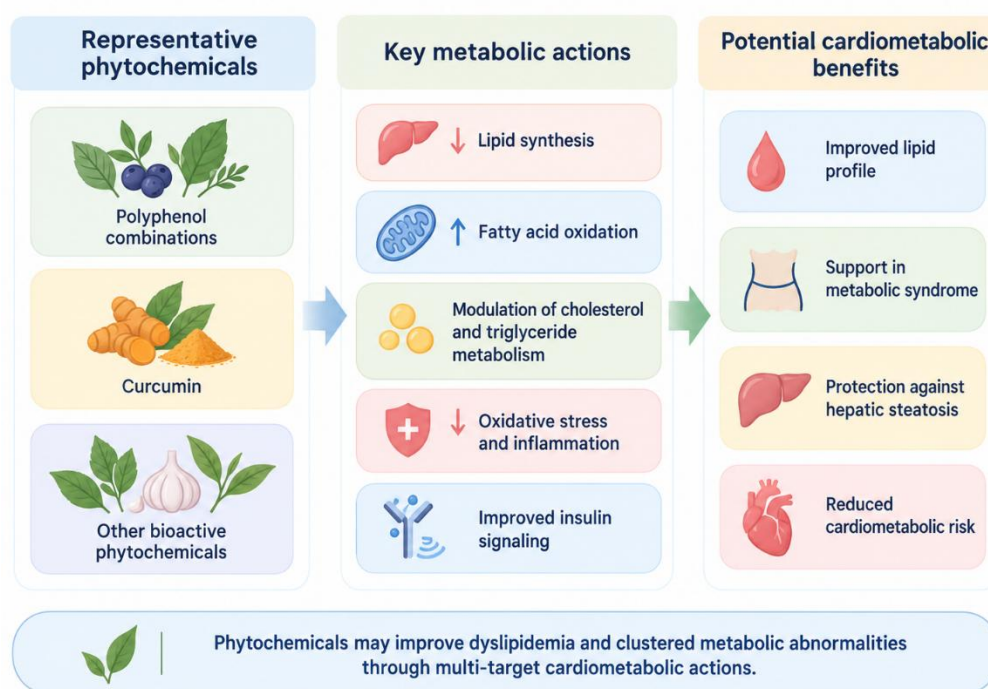


Figure 2: Cardiometabolic effects of phytochemicals in metabolic disorders

2.6 Phytochemicals in Steatotic Liver Disease

Metabolic dysfunction-associated steatotic liver disease is tightly associated with insulin resistance, hepatic lipid accumulation, oxidative stress, inflammation and energy regulation dysfunction in the cells. These processes are believed to be regulated by phytochemicals which involve suppressing lipogenic signalling, activating fatty acid oxidation, and dampening inflammatory and oxidant pathways that could lead to liver damage (Nisar et al., 2023). Epigenetics also plays a role, as several plant-based compounds have been shown to affect gene expression by DNA methylation, histone

modifications, and other epigenetic processes linked to obesity and metabolic dysfunction (Saad et al., 2021).

Mechanistic evidence for these effects also comes from plant sources that contain polyphenols. The components in pomegranate have been seen to possess antioxidant, anti-inflammatory, glucose-regulating, and lipid-modulating effects which can help maintain metabolic homeostasis (Maphetu et al., 2022). These activities may be significant as hepatic disease is often accompanied by abnormalities in skeletal muscle and adipose tissue, resulting in a wider system of defective glucose/lipid metabolism.

The relevance of skeletal muscle is highlighted by the fact that loss of muscle mass and dysfunction of the mitochondria can contribute to insulin resistance and glucolipid dysfunction. The preliminary evidence suggests that phytochemicals can help mitigate muscle loss by influencing oxidative stress, mitochondrial health, inflammatory responses, protein synthesis, and energy-sensing mechanisms (Li et al., 2025). Altogether, the results indicate that phytochemicals might exert multi-organ metabolic actions; however further clinical data are needed to elucidate the therapeutic potential of these compounds in liver disease and related systemic complications. The major hepatic and extrahepatic effects of phytochemicals are summarised in Table 2.

Table 2: Phytochemical mechanisms in liver and systemic metabolic dysfunction.

Target/compl ication	Principal phytochemical action	Potential metabolic relevance	References
Hepatic lipid accumulation	Suppression of lipogenic signaling and enhancement of fatty acid oxidation	May reduce hepatic steatosis and improve lipid handling	Nisar et al. (2023); Saad et al. (2021)
Oxidative stress	Reduction of reactive oxygen species and reinforcement of antioxidant defenses	May limit hepatocellular injury and metabolic stress	Nisar et al. (2023); Maphetu et al. (2022)
Inflammatory signaling	Attenuation of pro-inflammatory pathways	May reduce chronic hepatic and systemic inflammation	Nisar et al. (2023); Maphetu et al. (2022)
Epigenetic regulation	Modulation of DNA methylation and histone-related mechanisms	May alter expression of genes linked to obesity and metabolic dysfunction	Saad et al. (2021); Nisar et al. (2023)
Glucose homeostasis	Regulation of glucose-related metabolic pathways	May support improved glycemic balance	Maphetu et al. (2022); Saad et al. (2021)
Skeletal muscle	Modulation of protein turnover and pathways associated with muscle	May help preserve muscle mass	Li et al. (2025); Nisar

integrity	atrophy	in glucolipid metabolic disorders	et al. (2023)
Mitochondrial function	Protection of mitochondrial integrity and energy-sensing pathways	May improve cellular energy metabolism and insulin responsiveness	Li et al. (2025); Saad et al. (2021)
Multi-organ metabolic dysfunction	Coordinated effects across liver, skeletal muscle, and adipose-related pathways	Supports a systems-level approach to metabolic disease management	Li et al. (2025); Maphetu et al. (2022)

2.7 Pharmacological Evidence, Clinical Translation, Safety, and Future Perspectives

Many phytochemicals are able to modulate oxidative stress, inflammation, insulin signaling, lipid metabolism, mitochondrial function, and other pathways involved in metabolic disease, making them of great pharmacological potential. Fraxin's pleiotropic effects are exemplified by antioxidant, anti-inflammatory, cytoprotective and metabolic properties, primarily in the experimental model (Ferdous et al., 2024). The actions of phytochemicals in obesity, such as those related to adipogenesis, lipid handling, energy expenditure and inflammatory signalling, have all been reported for multi-target phytochemicals (Rao, 2025).

The one big constraint is that mechanisms of action and in vivo efficacy have not always translated in clinical settings. The variability of participant characteristics, phytochemical dose, formulation, intervention length, comparator groups, and outcome measures in human studies limits the ability to reproduce and draw meaningful comparisons across studies (Rao, 2025). The clinical application is further hampered by low oral bioavailability, high metabolism, limited tissue exposure and lack of standardisation of botanical preparations (Ghosh et al., 2021). Safety evaluation should be given increased consideration as adverse effects or drug-phytochemical interactions can be different depending on the dosage, formulation, comorbidities and other medications taken.

Chemically standardised preparations, pharmacokinetic characterisation, dose-response relationships and sufficiently powered RCTs with clinically relevant endpoints should be the focus of future studies. Stability, absorption, and target tissue exposure of compounds with low bioavailability can be enhanced by novel delivery methods (Pham et al., 2020). Therefore, there is a need for a more robust incorporation of both pharmacological and toxicological data with clinical evidence for successful, sustainable use of phytochemicals in the clinical treatment of metabolic disease.

3. Conclusion

The current review shows that the phytochemicals have a wide range of metabolic advantages through coordinated actions on insulin signaling, glucose and lipid metabolism, oxidative stress, inflammation, mitochondrial function, adipocyte biology and epigenetic regulation. Some polyphenols, flavonoids, anthocyanins, curcuminoids, phytosterols, terpenoids and related compounds of plant origin have been found to be

particularly promising in obesity, type 2 diabetes mellitus, dyslipidaemia, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease. Their multi-target actions are pharmacologically attractive as metabolic disorders are not mediated by single pathogenic pathways, but rather by multiple pathways. The preclinical data consistently corroborate these mechanisms, and emerging clinical data indicate that these mechanisms may provide benefits as supplemental strategies. Variable bioavailability, formulation differences, inconsistent dosing, varying study designs, lack of standardisation, and lack of long-term safety data for translation into routine care. There is a need for adequately powered randomized trials, clinically relevant dose-response studies, and chemically characterised preparations in the future which must be prioritised. Greater synergy between mechanistic, toxicological and clinical proof will be required to identify phytochemicals that have proven therapeutic activity in metabolic disease management that is repeatable.

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