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Polyphenolic Compounds from Natural Products in the Dual Management of Obesity and Diabetes: Mechanistic Insights and Therapeutic Potential

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ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) are tightly interlinked metabolic disorders characterized by insulin resistance, chronic low-grade inflammation, and dysregulated energy homeostasis. Together they form a convergent pathophysiological entity often termed "diabesity." Mounting evidence implicates dietary polyphenols diverse phytochemicals found in fruits, vegetables, teas, cocoa, whole grains, herbs, and spices as promising multi-target modulators of diabesity. This review synthesizes current knowledge on the chemical classes of polyphenols and integrates mechanistic insights spanning appetite regulation, digestive enzyme inhibition, adipogenesis and lipolysis, browning/thermogenesis, insulin signaling, incretin biology, hepatic glucose and lipid metabolism, gut microbiota remodeling, antioxidative and anti-inflammatory pathways, endothelial function, and β-cell protection. We discuss pharmacokinetics and bioavailability challenges (including the pivotal role of the microbiome), safety considerations, clinical evidence to date, and translational strategies such as synergistic combinations, food design, and novel delivery systems. Finally, we outline research gaps and pragmatic recommendations for leveraging polyphenols as adjuncts to lifestyle therapy and standard pharmacotherapy for obesity and T2DM.

Keywords: polyphenols; diabesity; insulin resistance; AMPK; gut microbiota

INTRODUCTION

The global syndemic of obesity and type 2 diabetes mellitus (T2DM), often referred to collectively as "diabesity," represents one of the greatest public health challenges of the 21st century[1, 2]. The parallel rise of these conditions has placed an enormous burden on health systems worldwide, not only through direct medical costs but also through indirect losses in productivity and quality of life. Both obesity and T2DM are intricately linked with increased risks of cardiovascular disease, certain cancers, and neurodegenerative disorders, thereby amplifying the complexity of their clinical management[3–5]. Current therapeutic approaches, including the use of pharmacological agents such as GLP-1 receptor agonists and SGLT2 inhibitors, as well as surgical interventions like bariatric procedures, have advanced patient outcomes significantly[6–8]. However, these options are often limited by cost, accessibility, long-term adherence, and side effect profiles, underscoring the urgent need for complementary and sustainable strategies.

Nutritional interventions enriched with bioactive compounds provide a promising avenue, as they can be integrated into daily dietary patterns with relative ease and minimal adverse effects[9]. Among these bioactive agents, polyphenols have attracted particular attention due to their diverse structures, abundance in commonly consumed plant-based foods, and broad range of biological activities. Polyphenols constitute a large family of secondary plant metabolites, including flavonoids, phenolic acids, stilbenes, lignans, tannins, and curcuminoids[10–12]. Their pleiotropic mechanisms enable them to influence multiple metabolic pathways simultaneously, addressing the multifactorial pathophysiology of diabesity. These mechanisms include antioxidative, anti-inflammatory, insulin-sensitizing, and lipid-modulating effects, as well as interactions with the gut microbiome and modulation of inter-organ communication[13–15].

Importantly, the efficacy of polyphenols is not uniform but instead depends heavily on host-specific factors. Genetic background, gut microbiome composition, hepatic metabolic capacity, and habitual dietary patterns collectively shape the bioavailability and biological effects of these compounds[16]. For example, inter-individual variability in gut microbial metabolism can determine whether a particular polyphenol is converted

into a bioactive metabolite capable of exerting therapeutic effects. This context-dependency highlights the need for precision nutrition approaches when considering polyphenols as therapeutic adjuncts for diabesity[17, 18]. Overall, the integration of polyphenols into dietary strategies offers a scientifically grounded and potentially cost-effective means of mitigating the global burden of obesity and T2DM, complementing existing pharmacological and surgical interventions with a focus on long-term health maintenance and disease prevention.

2. Chemical Classes of Polyphenols and Representative Dietary Sources

Polyphenols encompass a wide array of chemical classes, each distinguished by specific structural motifs that dictate their chemical reactivity, bioavailability, and biological activity[19, 20]. Among the most extensively studied are flavonoids, which themselves comprise several subclasses, including flavanols, flavonols, flavones, flavanones, isoflavones, and anthocyanins. Flavanols such as catechins are abundant in green tea and cocoa and are well known for their antioxidant and vascular protective properties. Flavonols like quercetin, found in onions and apples, have demonstrated anti-inflammatory and lipid-lowering effects[21, 22]. Flavones such as apigenin, typically sourced from parsley and celery, have shown promise in modulating cellular signaling pathways[23–25]. Flavanones, represented by hesperidin in citrus fruits, are recognized for their cardioprotective potential. Isoflavones such as genistein from soy exert estrogenic activity, influencing both metabolic and bone health, while anthocyanins, present in berries, contribute not only to their vivid colors but also to improved glycemic control and vascular function[26].

Phenolic acids represent another important group, primarily categorized into hydroxycinnamic acids and hydroxybenzoic acids. Chlorogenic acid, a hydroxycinnamic acid abundant in coffee, exerts glucose-lowering effects by modulating intestinal glucose absorption and hepatic glucose production[27]. Hydroxybenzoic acids such as gallic acid, commonly found in tea and berries, possess strong antioxidative activity and contribute to gut microbiome modulation. Stilbenes, although less widespread in nature, have attracted considerable scientific interest due to resveratrol, found in grapes and red wine, which has been associated with improved insulin sensitivity and cardiovascular health. Its structural analog, pterostilbene from blueberries, exhibits even greater bioavailability and similar metabolic benefits[28].

Lignans, present in seeds such as flaxseed and sesame, are metabolized by the gut microbiota into enterolignans with weak estrogenic activity that contribute to lipid regulation and cardiovascular protection[29]. Tannins, comprising hydrolyzable ellagitannins and condensed proanthocyanidins, are found in foods like pomegranates, nuts, grapes, cranberries, and cocoa. These compounds modulate oxidative stress and inflammatory pathways and are extensively metabolized into urolithins and other bioactive metabolites by the gut microbiota. Finally, curcuminoids, with curcumin from turmeric as the most prominent member, represent a unique group of diarylheptanoids with powerful anti-inflammatory, antioxidant, and metabolic regulatory properties[30, 31].

The diversity of these chemical classes is not merely academic but has practical implications for their health effects. Differences in redox chemistry, solubility, lipophilicity, and conjugation patterns strongly influence intestinal absorption, hepatic metabolism, plasma half-life, and tissue distribution[32]. Consequently, the biological activity of polyphenols cannot be generalized but must be understood in the context of their structural class and source, highlighting the importance of dietary diversity in maximizing their collective health benefits[33].

3. Pathophysiological Rationale: Why Polyphenols for Diabesity?

The rationale for employing polyphenols in the management of diabesity is rooted in the complex and multifactorial nature of the condition. At its core, diabesity arises from a chronic imbalance between caloric intake and energy expenditure, leading to adipose tissue expansion and ectopic lipid deposition in metabolic organs such as the liver and skeletal muscle[34, 35]. This excessive lipid accumulation disrupts mitochondrial function, resulting in oxidative stress and impaired energy metabolism. Concurrently, adipose tissue undergoes immune remodeling, with increased infiltration of macrophages and other immune cells that sustain a state of chronic low-grade inflammation[36, 37]. This inflammatory milieu exacerbates insulin resistance and impairs insulin signaling pathways, creating a vicious cycle of metabolic dysfunction.

Another critical element in diabesity is the impairment of pancreatic β-cell function, which compromises insulin secretion and eventually contributes to hyperglycemia [38]. Alongside this, gut dysbiosis and altered bile acid signaling further disturb metabolic homeostasis by influencing nutrient absorption, incretin secretion, and systemic inflammation[39–41]. These interconnected pathophysiological processes collectively drive the progression from obesity to T2DM and its associated complications. Addressing this web of dysfunction requires interventions capable of targeting multiple pathways simultaneously, an area where polyphenols demonstrate remarkable promise.Polyphenols exert their effects through several molecular mechanisms that intersect with key metabolic nodes[42, 43]. They modulate nutrient-sensing pathways such as AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1), both of which promote energy expenditure, mitochondrial biogenesis, and improved insulin sensitivity. They influence transcriptional regulators including peroxisome proliferator-activated receptors (PPARs), carbohydrate-responsive element-binding protein (ChREBP), and

sterol regulatory element-binding protein-1c (SREBP-1c), thereby modulating lipid and glucose metabolism at the gene expression level[44]. Furthermore, polyphenols improve inter-organ communication by influencing endocrine mediators such as adipokines, myokines, and incretins, all of which play central roles in energy homeostasis[18, 19, 34].

An additional advantage lies in their impact on the gut microbiome, where polyphenols act as prebiotics to selectively enrich beneficial bacterial populations while simultaneously reinforcing intestinal barrier integrity. These microbiome-mediated effects enhance systemic metabolic health and reduce inflammation. Taken together, the multifaceted actions of polyphenols allow them to target the major pathophysiological axes of diabesity simultaneously, offering a holistic therapeutic strategy that complements conventional pharmacological approaches[45]. Their integration into nutritional and therapeutic frameworks thus provides a rational, evidence-based pathway toward mitigating the global diabesity epidemic.

4. Mechanistic Landscape

4.1 Energy Intake and Appetite Regulation: Polyphenolic compounds exert important regulatory effects on appetite and energy intake through both central and peripheral mechanisms. Bioactive molecules such as cocoa flavanols, catechins, and anthocyanins have been shown to modulate the release of satiety-related hormones including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY)[46]. These hormones act synergistically to enhance satiety signaling, slow gastric emptying, and prolong the feeling of fullness after meals, thereby reducing overall caloric consumption. Moreover, polyphenol-rich foods, particularly those found in berries, legumes, and pulses, contribute significant amounts of dietary fiber that increase viscosity within the gastrointestinal tract[47]. This viscosity delays nutrient absorption and contributes further to satiety. In addition to physiological satiety signaling, polyphenols can influence hedonic aspects of eating behavior. Certain compounds have been reported to reduce the preference for high-sugar and high-fat foods, potentially through modulation of post-ingestive reward pathways in the brain[47-52]. By blunting hedonic responses and reward circuitry associated with palatable foods, polyphenols can limit overeating and emotional eating behaviors. These combined effects highlight the potential of polyphenolic compounds as natural appetite regulators that could be strategically utilized in dietary interventions aimed at reducing energy intake and preventing obesity and its associated metabolic complications.

4.2 Digestive Enzyme and Nutrient Absorption Modulation: Polyphenols play an important role in the modulation of digestive enzymes and nutrient absorption, providing a natural means of controlling postprandial metabolic responses. In carbohydrate metabolism, several classes of polyphenols, including flavonols such as quercetin, phenolic acids like chlorogenic acid, and tannins, have demonstrated inhibitory activity against key enzymes such as α-amylase and α-glucosidase[52-55]. By slowing the breakdown of complex carbohydrates, these compounds reduce the rate of glucose release and subsequently attenuate sharp increases in blood glucose following meals. Similarly, lipid digestion is influenced by the inhibitory effects of catechins, proanthocyanidins, and theaflavins on pancreatic lipase, an enzyme critical for triglyceride hydrolysis. Inhibition of lipase activity limits fat absorption and lowers circulating triglyceride levels[56-58]. Furthermore, some polyphenols interfere with bile acid activity, reducing micelle formation and thereby restricting lipid solubilization and uptake. Beyond enzymatic modulation, polyphenols can also downregulate intestinal glucose transporters such as SGLT1 and GLUT2, thereby reducing rapid glucose influx into the bloodstream[59-63]. This multifaceted regulation of nutrient digestion and absorption highlights polyphenols as valuable dietary agents in the prevention and management of obesity and diabetes, offering a complementary strategy to pharmacological inhibitors currently used for glycemic and lipid control.

4.3 Adipocyte Biology and Thermogenesis: Polyphenols influence adipocyte biology by modulating processes such as adipogenesis, lipolysis, fatty acid oxidation, and thermogenesis. During the differentiation of preadipocytes into mature adipocytes, transcription factors including C/EBPα and PPARγ play central roles in promoting fat storage[64-65]. Many polyphenolic compounds, such as resveratrol, quercetin, and catechins, inhibit these transcriptional regulators, effectively reducing the formation of new adipocytes and limiting lipid accumulation. In addition to anti-adipogenic activity, polyphenols stimulate lipolysis and fatty acid oxidation, largely through activation of signaling pathways such as AMPK and SIRT1. These pathways enhance mitochondrial function by upregulating carnitine palmitoyltransferase 1 (CPT1), a key enzyme in β-oxidation, while simultaneously suppressing acetyl-CoA carboxylase (ACC) activity, thereby reducing lipogenesis[66-68]. A further metabolic advantage of polyphenols lies in their ability to promote the browning of white adipose tissue. Compounds like resveratrol, curcumin, and catechins have been shown to induce the expression of uncoupling protein 1 (UCP1), PRDM16, and PGC-1α, which are markers of brown adipose tissue activity[69-72]. This shift promotes thermogenesis and increases overall energy expenditure, contributing to weight management. Through these diverse mechanisms, polyphenols exert potent effects on adipose tissue dynamics, supporting their therapeutic potential in combating obesity and metabolic syndrome.

4.4 Insulin Signaling and Glucose Homeostasis: Polyphenols exert beneficial effects on glucose metabolism by enhancing insulin signaling pathways and restoring glucose homeostasis. A central mechanism involves the

improvement of insulin sensitivity in skeletal muscle and adipose tissue. Compounds such as resveratrol, quercetin, and epigallocatechin gallate (EGCG) have been shown to restore IRS-1/PI3K/Akt signaling, leading to improved translocation of glucose transporter GLUT4 to the plasma membrane[73-74]. This facilitates glucose uptake by peripheral tissues and lowers circulating glucose levels. In the liver, polyphenols also regulate glucose production by inhibiting key gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase)[75-77]. Chlorogenic acid and curcumin, for example, are effective in suppressing hepatic gluconeogenesis, thereby reducing endogenous glucose output. Additionally, polyphenols influence incretin biology by promoting GLP-1 secretion from intestinal L-cells, often mediated through short-chain fatty acid production by gut microbiota. They can also inhibit the activity of dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for incretin degradation, thereby prolonging GLP-1 action and improving insulin secretion[78-82]. Collectively, these effects position polyphenols as potent natural agents in the regulation of glucose metabolism, offering benefits similar to pharmacological agents but with potentially fewer side effects.

4.5 Anti-inflammatory and Antioxidant Networks: The therapeutic potential of polyphenols in obesity and diabetes is closely tied to their ability to modulate inflammation and oxidative stress, two central mechanisms in metabolic dysfunction. Chronic low-grade inflammation within adipose tissue is a hallmark of obesity and insulin resistance. Polyphenols counteract this process by suppressing pro-inflammatory signaling pathways such as NF-κB, JNK, and the NLRP3 inflammasome [83-85]. This suppression reduces the secretion of cytokines including TNF-α, IL-6, and MCP-1, which are major drivers of insulin resistance and tissue dysfunction. In parallel, polyphenols strengthen cellular antioxidant defenses through activation of the Nrf2/ARE signaling pathway, leading to the upregulation of antioxidant enzymes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), superoxide dismutase (SOD), and glutathione peroxidase (GPx)[86]. These enzymes mitigate mitochondrial and endoplasmic reticulum stress, thereby preserving cellular function. Polyphenols also enhance endothelial function by improving nitric oxide (NO) bioavailability, reducing oxidative stress, and promoting vascular relaxation [87]. These vascular benefits are critical in mitigating the heightened cardiometabolic risk associated with obesity and diabetes. Taken together, the anti-inflammatory and antioxidant actions of polyphenols create a more favorable metabolic environment, supporting their use in disease prevention and management.

4.6 Pancreatic Islet Preservation: Polyphenols play a significant role in the preservation of pancreatic islet function, particularly in protecting β-cells from damage induced by glucolipotoxicity. Chronic exposure to high glucose and fatty acid levels leads to the overproduction of reactive oxygen species (ROS), endoplasmic reticulum (ER) stress, and eventual apoptosis of β-cells, all of which compromise insulin production and secretion[60]. Polyphenols mitigate these effects by enhancing antioxidant defenses and reducing oxidative stress within islet cells. They modulate apoptotic pathways by upregulating anti-apoptotic proteins such as Bcl-2 while downregulating pro-apoptotic proteins like Bax, thereby maintaining cell viability[61]. In addition, polyphenols influence the PERK/eIF2α signaling pathway, which plays a key role in ER stress responses, helping to restore protein-folding homeostasis. Beyond protective effects, some polyphenols have also been shown to enhance the glucose-stimulated insulin secretory response, thereby supporting improved glycemic control[61]. This dual ability to preserve β-cell integrity and optimize insulin secretion positions polyphenols as valuable dietary components for preventing the progressive decline in β-cell function observed in type 2 diabetes[61]. Their role in pancreatic health underscores their therapeutic relevance in long-term diabetes management strategies.

4.7 Gut Microbiota and Intestinal Barrier: Polyphenols exert profound effects on gut microbiota composition and intestinal barrier integrity, thereby contributing to improved metabolic health. Many polyphenolic compounds are poorly absorbed in the small intestine and reach the colon, where they act in a prebiotic-like manner[62]. Non-absorbed polyphenols and their metabolites promote the growth of beneficial microbial taxa such as Akkermansia muciniphila and Bifidobacterium species, while simultaneously increasing the production of short-chain fatty acids (SCFAs). These SCFAs not only improve metabolic flexibility but also stimulate GLP-1 secretion, enhancing insulin secretion and glucose control[63]. Importantly, gut microbiota metabolize polyphenols into smaller compounds, such as urolithins from ellagitannins and phenyl-γ-valerolactones from procyanidins, which often display greater systemic bioactivity and bioavailability than their parent molecules. Polyphenols also strengthen the intestinal barrier by reinforcing tight-junction proteins, reducing gut permeability and limiting the translocation of lipopolysaccharides (LPS) into circulation. By lowering endotoxemia and associated metabolic inflammation, they support a healthier metabolic profile[64]. These combined actions highlight the gut as a central mediator of polyphenol benefits, underscoring the importance of diet-microbiota interactions in the prevention and management of obesity, diabetes, and related metabolic disorders.

5. Safety and Interactions

Dietary polyphenols are widely considered safe when consumed through foods at nutritional doses, but certain considerations are important, particularly with high-dose supplements or concentrated extracts. One key issue is drug interactions, as polyphenols can modulate cytochrome P450 enzymes and transporters such as OATP and P-glycoprotein, potentially altering the pharmacokinetics of drugs like warfarin, statins, or antidiabetic agents[65]. Excessive intake of tannin-rich beverages, such as black tea, may interfere with non-heme iron absorption, raising concerns for individuals with marginal iron status. While rare, hepatotoxicity has been reported with high doses of green tea extracts or poorly regulated herbal products, underscoring the need for rigorous quality control. During pregnancy, lactation, or pediatric use, food-based polyphenols are preferred over supplements unless under medical supervision, given limited safety data[66]. Overall, while the risk profile is low, clinicians and researchers must account for dose, form, and potential interactions to ensure safe application.

6. Evidence from Human Studies

Clinical evidence for polyphenols in managing obesity and diabetes is steadily growing, with randomized controlled trials and meta-analyses providing insights despite considerable heterogeneity. Studies frequently demonstrate small but clinically meaningful improvements in glycemic control, including modest reductions in fasting glucose and HbA1c, particularly with anthocyanins, curcuminoids, and green tea extracts in populations with type 2 diabetes or metabolic syndrome[67]. Some trials report enhanced insulin sensitivity, measured through indices like HOMA-IR or more precise clamp studies, especially with resveratrol and advanced curcumin formulations. Regarding body composition, polyphenols tend to produce modest but consistent reductions in body weight, body mass index, or visceral fat when incorporated into calorie-restricted or Mediterranean-style diets. Improvements in cardiometabolic biomarkers, including lower triglycerides, reduced LDL cholesterol, better HDL functionality, decreased hs-CRP, and improved endothelial function, have also been observed[68]. However, variability across studies reflects differences in formulation, standardization, duration, baseline diet, and microbiome-related metabolism.

7. Synergy and Dietary Patterns

Polyphenols exert their most meaningful effects when consumed as part of whole dietary patterns rather than in isolation. The Mediterranean and DASH diets exemplify this synergy, as they combine diverse polyphenolic compounds with dietary fiber, monounsaturated and polyunsaturated fats, and essential micronutrients, creating cumulative benefits greater than single agents[69]. Food pairings also play an important role in bioavailability and effectiveness. For example, the absorption of curcumin is significantly enhanced by the presence of piperine from black pepper, while polyphenols in tea or cocoa interact with protein- and fat-rich matrices to influence postprandial metabolism.[69] Moreover, co-nutrients such as omega-3 fatty acids, magnesium, and vitamin D may augment the insulin-sensitizing and anti-inflammatory actions of polyphenols, reinforcing their role in metabolic health. Taken together, polyphenols act not as isolated pharmacological agents but as integral dietary factors, supporting the case for food-based approaches to managing obesity and diabetes.

8. Practical Summary for Clinicians and Researchers

Polyphenols represent a class of bioactive compounds with multi-target activity, influencing energy regulation, lipid and glucose metabolism, inflammatory processes, and vascular function, making them particularly relevant to the complexity of diabesity[70]. Their integration into clinical or public health strategies should prioritize food-based sources, as whole foods provide synergistic co-factors that enhance both efficacy and safety. Standardized extracts may be considered as adjuncts in specific phenotypes or clinical trial settings, though benefits tend to be modest when examined individually[70]. Importantly, the cumulative effect of sustained polyphenol intake as part of a comprehensive lifestyle plan, including balanced diet, physical activity, quality sleep, and pharmacotherapy when indicated, is likely to provide the greatest clinical impact. Substantial interindividual variability, influenced by genetics, baseline diet, and microbiome composition, underscores the need for personalization. Emerging precision nutrition strategies that integrate microbiome-informed approaches will likely shape the future of polyphenol-based interventions.

CONCLUSIONS

Polyphenolic compounds from natural products constitute a scientifically plausible and clinically promising adjunct for the dual management of obesity and T2DM. Through convergent actions on digestive processes, adipocyte biology, thermogenesis, insulin signaling, hepatic metabolism, inflammatory and oxidative stress pathways, vascular function, and the gut microbiota, polyphenols can modestly but consistently improve key metabolic endpoints. Translation to practice favors a food-first approach embedded in healthy dietary patterns, with targeted use of standardized, bioavailability-enhanced formulations in selected patients. Continued rigor in trial design, biomarker depth, and personalization strategies will clarify who benefits most and how to deploy these agents effectively and safely.

ABBREVIATIONS

ACC, acetyl-CoA carboxylase;
AMPK, AMP-activated protein kinase;

ARE, antioxidant response element;
ChREBP, carbohydrate response element-binding protein;
CPT1, carnitine palmitoyltransferase-1;
DPP-4, dipeptidyl peptidase-4;
ER, endoplasmic reticulum;
FMD, flow-mediated dilation;
G6Pase, glucose-6-phosphatase;
GLP-1, glucagon-like peptide-1;
HbA1c, glycated hemoglobin;
HOMA-IR, homeostatic model assessment of insulin resistance;
JNK, c-Jun N-terminal kinase;
MUFA, monounsaturated fatty acid;
NAFLD/NASH, non-alcoholic fatty liver disease/steatohepatitis;
NF-κB, nuclear factor-κB;
NO, nitric oxide;
NQO1, NAD(P)H quinone dehydrogenase 1;
Nrf2, nuclear factor (erythroid-derived 2)-like 2;
PEPCK, phosphoenolpyruvate carboxykinase;
PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α;
PI3K, phosphoinositide 3-kinase;
PPAR, peroxisome proliferator-activated receptor;
PRDM16, PR domain-containing 16;
PYY, peptide YY;
ROS, reactive oxygen species;
SCFA, short-chain fatty acid;
SGLT1/GLUT2, sodium-glucose/ facilitative glucose transporters;
SIRT1, sirtuin-1;
SREBP-1c, sterol regulatory element-binding protein-1c;
TG, triglyceride;
T2DM, type 2 diabetes mellitus;
UCP1, uncoupling protein-1;
UGT/SULT/COMT, UDP-glucuronosyltransferase/sulfotransferase/catechol-O-methyltransferase.

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