



REVIEW ARTICLE

Molecular mechanisms and translational therapeutic potential of plant-derived bioactives in metabolic and neurodegenerative disorders

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Abstract

Metabolic disorders and neurodegenerative diseases have emerged as a set of interrelated disorders caused by inflammatory processes, oxidative stress, mitochondrial impairment and disruption of cellular signalling mechanisms. Metabolic disorders like obesity and type 2 diabetes, along with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are characterized by common molecular mechanisms that include insulin resistance, neuroinflammation, dysregulation of energy metabolism and cellular damage. Natural bioactive compounds from plants have gained significant attention in scientific circles because of their potential to target several mechanisms at once. Phytochemicals like polyphenols, flavonoids, alkaloids, terpenoids and saponins exhibit antioxidant, anti-inflammatory, neuroprotective and metabolic activities. Bioactive compounds like curcumin, resveratrol, quercetin, epigallocatechin gallate and berberine modulate important signalling pathways like NF- κ B, AMP-activated protein kinase (AMPK), PI3K/Akt, MAPK, Nrf2 and SIRT1. Nonetheless, even with promising experimental data, there are limitations associated with poor bioavailability, fast metabolism, unpredictable pharmacokinetics and lack of large-scale clinical studies. It is important to mention that some phytochemicals exhibit dose-dependent and context-dependent actions, which could suggest variations in efficacy depending on the condition being treated. There are novel approaches involving nanotechnology, bioenhancers, alteration of gut microbiota composition and precision nutrition approaches that have been proposed for solving these translational challenges. This review discusses the molecular mechanisms by which phytochemicals modulate metabolism, inflammation and neurodegeneration, but it also includes the existing limitations and contradictory results regarding these compounds.

Keywords

Alzheimer's disease; chronic inflammation; gut microbiota; metabolic disorders; molecular signaling; neurodegeneration; oxidative stress; phytochemicals; plant bioactives; translational therapeutics

Introduction

Metabolic diseases and neurodegenerative diseases are two prominent health issues in today's world, which show an alarming rate of rising prevalence across the globe. Obesity, type 2 diabetes mellitus, metabolic syndrome, Alzheimer's disease (AD) and Parkinson's disease (PD) constitute significant health and socioeconomic problems in contemporary society (1). Despite their conventional studies as independent disorders, there is accumulating research highlighting the fact that these diseases share common pathogenesis involving inflammation, oxidative stress, mitochondrial malfunctioning, insulin resistance and impaired cellular metabolism (2, 3). The continuous activation of inflammation pathway plays an important role in the development of

metabolic and neurodegenerative diseases. The high level of pro-inflammatory cytokine molecules such as TNF- α , IL-6 and NF- κ B causes insulin resistance, dysfunction of endothelium cells, synapses and neurons (4). The activation of microglia cells in the brain leads to neuroinflammation and loss of neurons, especially in Alzheimer's and Parkinson's diseases (5). At the same time, overproduction of reactive oxygen species (ROS) molecules causes damage to lipids, proteins and nucleic acid molecules (6). The conventional drug treatment options available for metabolic and neurodegenerative diseases only offer symptomatic benefits without addressing the complex molecular mechanism behind the development of these conditions. Prolonged use of artificial pharmaceuticals might also pose several side effects and loss of efficacy and patient adherence (7). Thus, there has been an increased focus on the use of natural bioactive compounds that can act on different disease pathologies.

The natural active components from plants show multifunctional pharmacological activity, including antioxidative, anti-inflammatory, anti-apoptotic and neuroprotective effects (8). Natural substances like polyphenolic acids, flavonoids, alkaloids, terpenoids and saponins can effectively control the signalling pathways involved in metabolism, inflammation, oxidative stress and neuron survival (9). Bioactive agents such as curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG) and berberine can act on AMP-activated protein kinase (AMPK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), nuclear factor erythroid 2-related factor 2 (Nrf2) and sirtuin-1 (SIRT1) pathways (10). Nevertheless, despite the promising results of experiments, the practical use of phytochemicals faces several problems due to poor oral bioavailability, fast metabolism, low permeation of blood-brain barrier, heterogeneity of phytochemicals and lack of comprehensive validation in clinical practice (11). Moreover, some phytochemicals may have opposite effects at different doses, thereby stressing the importance of critical analysis of therapy outcome instead of merely descriptive description of effects (12). In contrast to other reviews concentrated

mostly on the study of separate phytochemicals and one specific disease, the current review addresses metabolic disorders, chronic inflammation and neurodegeneration as components of one mechanism. Special attention is paid to interactions between signalling pathways, translational limitations, interactions of gut-brain-metabolism axis and perspectives in developing nano formulations and therapy. Fig. 1 provides a schematic overview of the molecular crosstalk linking metabolic dysfunction with neurodegenerative progression.

Classification of plant-derived bioactive compounds

Plant-originated bioactive compounds known as phytochemicals are secondary plant metabolites that have been produced by plants through natural metabolic processes for self-protection and adaptation. They exhibit various medicinal effects and can be categorized into polyphenols, alkaloids, terpenoids, glycosides and saponins based on their structural and biological sources (13).

Polyphenols

Polyphenols have been one of the most studied phytochemicals due to their high antioxidative and anti-inflammatory effects. They include flavonoids, stilbenes, phenolic acids and lignans (14). Quercetin, kaempferol and catechin inhibit inflammatory pathways like NF- κ B and MAPK pathways, thus lowering oxidative stress and inflammation (15). Stilbenes like resveratrol are mostly found in grapes, where they help activate the SIRT1 and AMPK pathways, contributing to mitochondrial biogenesis and metabolic function (16).

Alkaloids

Alkaloids are substances that contain nitrogen and have pharmacological properties. Berberine is a specific type of isoquinoline alkaloid that has positive effects on insulin sensitivity and glucose metabolism via AMPK signalling (17). Some alkaloids also possess neuroprotective properties by affecting neurotransmitters and decreasing oxidative stress. Nevertheless, certain alkaloids may cause toxicity at high concentrations.

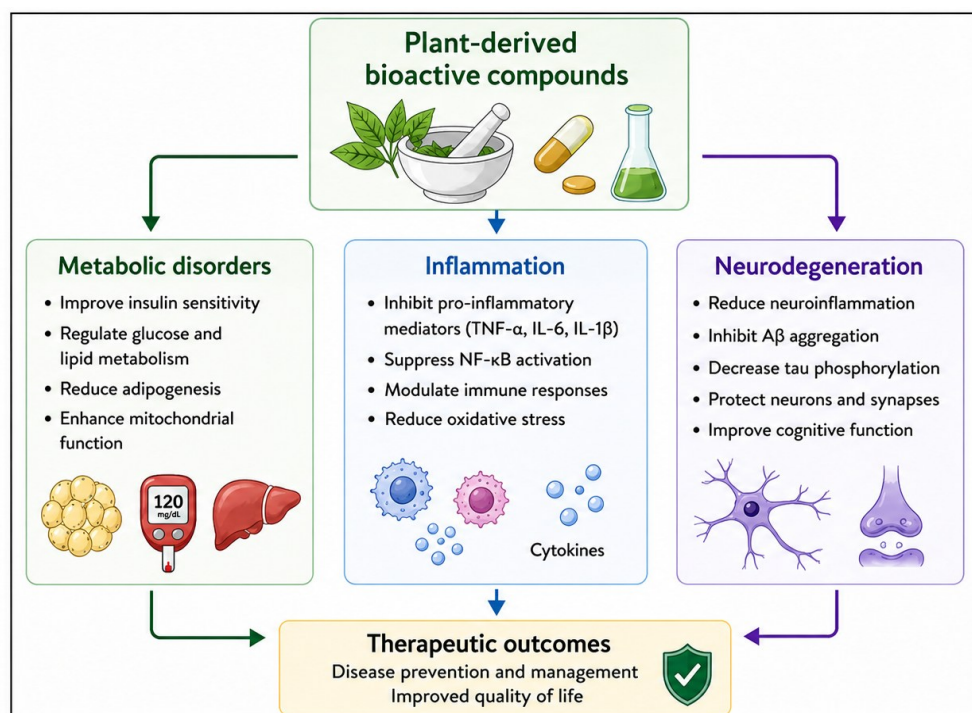


Fig. 1. Schematic representation of the multi-target therapeutic effects of plant-derived bioactive compounds in modulating metabolism, inflammation and neurodegeneration through key signalling pathways such as AMPK, NF- κ B, PI3K/Akt and Nrf2.

Terpenoids

The terpenoids have varied chemical structures and originate from isoprene units. Curcumin isolated from *Curcuma longa* has potent antioxidative and anti-inflammatory effects through mechanisms involving NF- κ B, Nrf2 and cytokine signalling pathways (18). The terpenoids also play important roles in mitochondrial and redox balance regulation.

Glycosides and Saponins

The biological activity of glycosides and saponins is very wide-ranging; it involves hypocholesterolaemia, immune modulating, antioxidative and neuroprotective actions (19). Ginsenosides extracted from ginseng enhance neuron survival through mitochondrial pathways, neurotransmitter secretion and antioxidants (20).

Role of plant-derived bio actives in metabolic regulation

The metabolic diseases like obesity, insulin resistance, type 2 diabetes mellitus and dyslipidemia include features of disturbed energy metabolism, inflammation and oxidative stress (21). The plant-based bioactive substances are considered as the most effective regulators of metabolic pathways because they are potent to target multiple molecules. The effectiveness of phytochemicals in the treatment of metabolic diseases can be attributed to the capability of phytochemicals to target multiple interconnected molecular pathways associated with inflammation, oxidative stress, mitochondrial dysfunction and metabolic modulation. Curcumin, resveratrol, quercetin, EGCG and berberine are some of the phytochemicals targeting different signalling pathways at once, resulting in multifunctional pharmacologic effects in metabolic and neurodegenerative diseases. Some major targets and biological activities of the mentioned phytochemicals are listed in Table 1. In conclusion, all the above-mentioned studies suggest that phytochemicals demonstrate multitarget modulatory effects allowing for simultaneous regulation of inflammatory, metabolic, oxidative and neurodegenerative pathways.

Regulation of glucose homeostasis and insulin sensitivity

Insulin resistance is a distinctive characteristic of metabolic syndrome and type 2 diabetes mellitus. The interference with the insulin receptor signal pathway, especially IRS and PI3K/Akt, plays an important role in the impairment of glucose transport and metabolic dysregulation (22).

The enhancement of insulin sensitivity by several phytochemicals occurs via stimulation of metabolic pathways. For instance, berberine increases the rate of glucose uptake and

enhances insulin signalling by activating AMPK that acts as the major regulator of cellular energy metabolism (23). Quercetin improves insulin sensitivity by stimulating GLUT4 translocation in muscle tissues leading to enhanced glucose transport (24).

The effect of resveratrol on glucose metabolism involves the activation of SIRT1 and AMPK signalling pathways which lead to better mitochondrial performance and insulin sensitivity (25). Epigallocatechin gallate derived from green tea is another agent known to alleviate insulin resistance caused by oxidative stress. Nonetheless, conflicting results have been observed from various clinical studies. While experimental studies usually indicate significant metabolic advantages, some human trials have indicated that phytochemicals offer only minor advantages in terms of their effect on blood sugar levels (26). Possible explanations for such disparities might be the differences in dosage, availability, patients' metabolic conditions, time period and study design.

Modulation of lipid metabolism

Abnormal regulation of lipid metabolism is linked to several pathologies such as obesity, cardiovascular disease and metabolic syndromes. Various bioactive compounds derived from plant sources help control lipids metabolism by modulating fatty acids synthesis, oxidation and fat cell development (27).

Bioactive polyphenols such as EGCG suppress sterol regulatory element-binding proteins (SREBP) that act by modulating gene transcription related to fatty acid biosynthesis (28). At the same time, activation of AMPK increases fatty acids oxidation and decreases lipids accumulation in metabolic tissues. Another active compound, curcumin, controls peroxisome proliferation-activated receptors (PPAR- α & PPAR- γ) involved in adipocytes development and lipid metabolism (29). Although there is a growing body of experimental evidence on the beneficial effect of various phytochemicals in regulating lipid metabolism, insufficient long-term clinical data on their effectiveness is available. It has been observed that their effects might depend on diet composition, presence of obesity and other metabolic diseases (30). Thus, further clinical trials should be carried out to confirm their therapeutic effectiveness.

Anti-obesity effects and energy homeostasis

Obesity arises due to excessive fat storage in response to an imbalance between energy uptake and output. Various phytochemicals affect energy balance by modulating appetite, thermogenesis, fat cell differentiation and mitochondrial functioning

Table 1. Multi-target molecular mechanisms of major phytochemicals in metabolic and neurodegenerative disorders

Phyto chemical	Major molecular targets	Principal signalling pathways	Therapeutic effects	Major disease applications
Curcumin	NF- κ B, Nrf2, COX-2, PI3K/Akt	NF- κ B, MAPK, Nrf2	Anti-inflammatory, antioxidant, anti-amyloidogenic	Alzheimer's disease, obesity, diabetes
Resveratrol	SIRT1, AMPK, PGC-1 α	AMPK/SIRT1, PI3K/Akt	Mitochondrial protection, insulin sensitization, neuroprotection	Parkinson's disease, metabolic syndrome
Quercetin	GLUT4, Nrf2, MAPK	PI3K/Akt, MAPK, Nrf2	Antioxidant, anti-apoptotic, glucose regulation	Diabetes, neurodegeneration
EGCG	NF- κ B, ROS, mitochondrial enzymes	MAPK, Nrf2	ROS scavenging, anti-inflammatory activity	Parkinson's disease, obesity
Berberine	AMPK, IRS, GLUT4	AMPK signaling	Improved glucose uptake and lipid metabolism	Type 2 diabetes mellitus
Ginsenosides	Bcl-2, mitochondrial proteins	PI3K/Akt	Anti-apoptotic and neuroprotective activity	Neurodegenerative disorders

(31). Catechins and capsaicin promote thermogenesis by activating brown adipose tissue and upregulating uncoupling proteins (UCPs), thus increasing energy expenditure (32). On the other hand, resveratrol and curcumin suppress adipocyte development by inhibiting transcription factors like CCAAT/enhancer-binding protein alpha (C/EBP α) and PPAR- γ (33).

Besides, specific phytochemicals facilitate mitochondrial biogenesis and oxidative phosphorylation and therefore boost cellular energy production. However, there is no concrete evidence of their use in humans because some of the anti-obesity effects established in experimental animals have not been reproduced clinically.

Gut microbiota and metabolic regulation

Gut microbiota has been implicated to be crucial for metabolic regulation and inflammation in recent research (34). Gut dysbiosis has been associated with obesity, insulin resistance and endotoxemia. Polyphenols from plant sources act as prebiotic substances that regulate the gut microbiome composition. Polyphenols encourage the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* species while inhibiting the growth of pathogens (35). Another outcome of the metabolism of polyphenols by the gut microbiota is the formation of short-chain fatty acids (SCFAs) that have an impact on the metabolism of glucose, improvement of intestinal integrity and control of inflammation. The role of gut microbiota in regulating the availability and activity of phytochemicals has also been identified. Nevertheless, the interactions between phytochemicals and the gut microbiota need more elucidation.

Anti-inflammatory mechanisms of plant-derived bio actives

Low-grade inflammation is well understood to be a core pathogenic mechanism that ties together both metabolic disease and neurodegeneration (36). While acute inflammation is physiologically beneficial, chronic inflammation leads to the development of insulin resistance, vascular dysfunction, mitochondrial dysfunction and neurodegeneration (37). Plant-derived natural products exhibit anti-inflammatory activity by influencing several signalling pathways related to cytokine secretion and oxidative stress.

Suppression of pro-inflammatory cytokines

Among the major anti-inflammatory effects of phytochemicals is their inhibition of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6 (38). Increased concentrations of these cytokines play a significant role in metabolic impairment and neuron degeneration.

Polyphenols like quercetin and resveratrol decrease cytokine expression through modulation of intracellular pathways responsible for inflammatory gene transcription (39). Curcumin has been extensively studied for its anti-cytokine effects in experimental and clinical settings (40). Inhibition of pro-inflammatory mediators leads to increased insulin sensitivity, endothelial function and survival of neurons.

However, some studies report variability in efficacy of anti-inflammatory activity due to dose-dependent effects and disease states (41). Some studies have revealed poor therapeutic response to phytochemical supplements in chronic inflammation, suggesting that phytochemical administration may not be sufficient to restore inflammatory damage.

Modulation of NF- κ B signalling pathway

NF- κ B pathway is known as one of the key regulators of inflammation-related gene expression and immunity (42). Activation of NF- κ B results in the transcription of cytokines, adhesion molecules, chemokines and inflammatory enzymes such as cyclooxygenase-2 (COX-2). Plant-based bioactive compounds target NF- κ B signalling through the blockade of I- κ B α degradation and consequently, NF- κ B nuclear translocation (43). Among the numerous phytochemicals that act against NF- κ B, curcumin, resveratrol and EGCG are the most studied ones. Blocking of NF- κ B signalling leads to decreased production of inflammatory mediators as well as diminished damage due to oxidative stress-related injuries. On the other hand, complete blockade of NF- κ B signalling might be counterproductive as it can negatively affect physiological immunity.

Inhibition of COX and LOX Pathways

The activity of COX and LOX enzymes is responsible for the production of inflammatory prostaglandins and leukotrienes (44). Over-expression of COX-2 has been noted in cases of chronic inflammation and neurodegeneration. Curcumin and other flavonoids and terpenoids, such as quercetin, can down-regulate COX-2 production and reduce the inflammatory response associated with these eicosanoids (45). In that respect, these compounds could serve as anti-inflammatory agents which work similarly to some non-steroidal anti-inflammatory drugs (NSAIDs) but without causing any harmful side effects on the gastrointestinal system.

Regulation of MAPK and JAK-STAT Signalling pathways

Pathways involving MAPK such as ERK, JNK and p38 MAPK play roles in regulating inflammation, oxidative stress, apoptosis and cell adaptations (46). Both resveratrol and catechins affect the MAPK pathway and prevent inflammation in metabolic and neurons through this pathway (47). Moreover, different plant compounds inhibit the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway, preventing cytokine-induced inflammation through this mechanism (48). Even though much is known about these potential mechanisms, more work needs to be done in understanding interactions among the MAPK, NF- κ B and oxidative stress pathways.

Inflammation as a link between metabolism and neurodegeneration

The link between metabolic diseases and neurodegeneration occurs through the mechanism of chronic inflammation (49). Metabolic inflammation leads to metabolic disorders such as insulin resistance and dysfunctional adipose tissue function. Neuroinflammation results in synaptic damage and neuronal death, causing neurodegeneration. Plant-based bioactive compounds have the remarkable potential of regulating inflammation at the systemic level and also modulating both metabolic and neuronal dysfunction by targeting multiple biological processes (50). Multi-targeting properties represent a major asset for treating complex diseases. Nevertheless, further research is needed to see how modulation of inflammatory signalling affects human health. Fig. 2 summarizes the principal intracellular signalling pathways targeted by major plant-derived bioactive compounds.

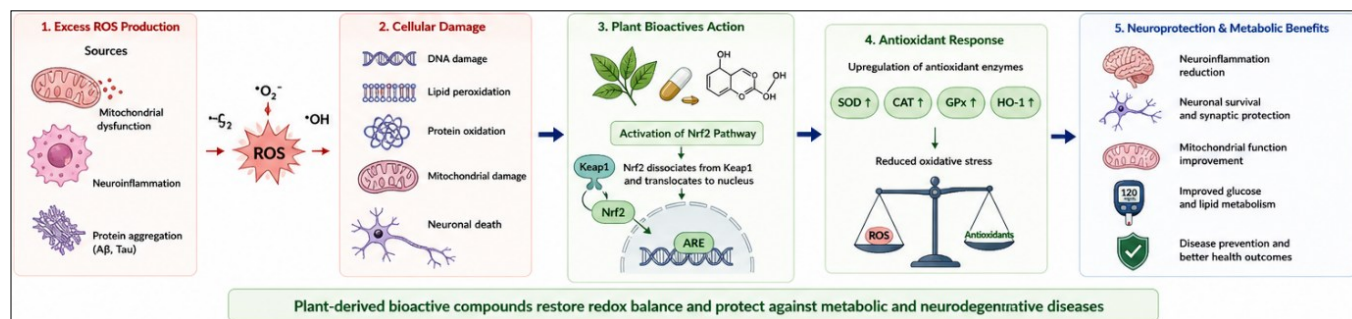


Fig. 2. Role of plant-derived bioactive compounds in modulating oxidative stress and promoting neuroprotection. Excessive production of reactive oxygen species (ROS) due to mitochondrial dysfunction, inflammation and protein aggregation leads to cellular damage, including lipid peroxidation, DNA damage and neuronal degeneration. Plant bio actives activate antioxidant defence mechanisms primarily through the Nrf2/ARE signalling pathway, resulting in upregulation of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and heme oxygenase-1 (HO-1). These effects collectively restore redox balance, reduce oxidative stress, enhance mitochondrial function and protect against neurodegenerative and metabolic disorders.

Neuroprotective effects of plant-derived bio actives in neurodegenerative disorders

Neurodegeneration involves progressive loss of neuronal function and permanent neuronal cell death, culminating in cognitive decline, motor dysfunction and neurological impairment (51). The two commonest neurodegenerative conditions are AD and PD, which exhibit several overlapping pathogenesises, such as oxidative stress, mitochondrial dysfunction, neuroinflammation, protein aggregation and cell signalling impairment (52). Plant bioactives have become popular due to their potential to act on numerous neurodegeneration mechanisms at once.

Alzheimer's Disease

Alzheimer's disease is a pathology associated with extracellular deposition of amyloid-beta ($A\beta$) plaques as well as intracellular formation of neurofibrillary tangles consisting of hyperphosphorylated tau protein (53). Such abnormalities are associated with disturbances in the functioning of synapses, mitochondria, neuronal cell death and loss of cognitive abilities. It was demonstrated experimentally that curcumin can prevent $A\beta$ protein aggregation and help in removing amyloid plaques from the brain (54). Resveratrol increases degradation of the amyloid protein fragments through stimulation of SIRT1-dependent proteasomal mechanisms and mitochondrial function (55). Other phytochemicals such as quercetin and EGCG were found to have antioxidative effects and decrease phosphorylation of tau protein via modulation of PI3K/Akt and ERK signalling (56). There are several studies conducted on human patients which demonstrated a lack of efficacy of natural products' treatment for AD due to low absorption and low activity of antioxidants within the blood-brain barrier (57). Additionally, differences in the participants' age, degree of pathology and duration of the experiment might play a certain role in the results obtained. Some recent experiments even suggested that the effectiveness of antioxidants could drop at later stages of neurodegeneration.

Parkinson's disease

Parkinson's disease mainly involves progressive loss of dopaminergic neurons in the substantia nigra and the formation of aggregates of the protein α -synuclein (58). Defective function of mitochondria, oxidative damage and inflammation are factors that play an important role in disease pathogenesis. The neuroprotective effects of polyphenolic compounds like resveratrol and catechins include the neutralization of ROS and promoting mitochondrial

biogenesis (59). The compound curcumin prevents α -synuclein aggregation and reduces neuronal apoptosis via anti-inflammatory action. Neuroprotection by the saponin class of molecules, the ginsenosides found in ginseng root extracts, has also been reported (60). However, some of the experimental observations have yet to be confirmed in large-scale human clinical trials.

Other neurodegenerative disorders

Aside from their beneficial effect on patients suffering from AD and PD, phytochemicals are known for their possible medicinal impact on Huntington's disease, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (61). Like other neurological conditions mentioned above, these ailments are characterized by oxidative stress, mitochondrial dysfunction, excitotoxicity and inflammation. Flavonoids and some polyphenols have been found to decrease glutamate-induced neurotoxicity via modulating apoptosis signalling pathways (62). Some phytochemicals also increase neuronal plasticity and synaptic performance. Despite numerous research studies, the evidence for the benefits of phytochemicals is still preclinical mostly.

Molecular mechanisms of neuroprotection

The bioactive components from plants have several neuroprotective mechanisms that are interlinked. They counteract the oxidative stress by stimulating the antioxidant systems of our body and inhibiting the formation of high levels of ROS (63). In addition, they prevent the development of neuroinflammation by inhibiting the NF- κ B and MAPK cascades and hence preventing the damaging effects of cytokines on neurons. Some phytochemicals also regulate apoptosis in the brain via controlling the functions of Bcl-2, caspases and mitochondrial membrane permeability (64). Activation of signalling pathways for neuroprotection involving PI3K/Akt, BDNF and SIRT1 also facilitates cell survival.

Moreover, phytochemicals have a wide range of activities such that they can address the problems of oxidative stress, inflammation, mitochondrial dysfunction and protein misfolding at once, which is highly advantageous considering the polygenic nature of neurological disorders.

Nevertheless, their use has limited translation due to pharmacokinetics challenges, individual response variations and lack of clinical studies. Future work should focus on validating the mechanisms, developing treatment approaches and refining delivery methods.

Oxidative stress and antioxidant defence mechanisms

One of the essential pathophysiological mechanisms associated with the development of both metabolic and neurodegenerative disorders is oxidative stress (65). Oxidative stress is caused by an imbalance in the rate of production of ROS and the inherent body's antioxidant defence mechanism. The harmful effects of oxidative stress include damage to lipids, proteins, mitochondrial membranes and nucleic acids due to excessive amounts of ROS (66). Metabolic diseases like obesity and type 2 diabetes mellitus have been linked to oxidative stress, which plays a key role in developing insulin resistance, endothelial dysfunction and chronic inflammation (67). Neurodegenerative diseases, such as AD and PD, are also affected by oxidative stress (68).

The plant-based bioactive substances act through protection mainly by increasing the antioxidative systems and decreasing the damage caused by reactive oxygen species. Some phytochemicals are free radical scavengers, whereas others control the pathways involved in antioxidation. Oxidative stress, inflammation, mitochondrial dysfunction and neurodegeneration are strongly associated with each other and together form the basis for progression of metabolic diseases as well as neurodegenerative diseases. These molecular pathways are linked to one another through interactions in which ROS formation, cytokine signalling and energy production play important roles. Pathological interactions between these processes, as well as the protection offered by phytochemicals against them, are listed in Table 2.

Activation of Nrf2 Signalling pathway

Nuclear factor erythroid 2-related factor 2 (Nrf2) is one of the key antioxidants regulators in antioxidant defence system (69). Under conditions of oxidative stress, Nrf2 separates from Kelch-like ECH-associated protein 1 (Keap1) and enters the cell nucleus, which stimulates the transcription of antioxidant and cytoprotective genes. The activation of Nrf2 signalling contributes to the upregulation of genes encoding for antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and heme oxygenase-1 (HO-1) (70). Curcumin, quercetin, EGCG and resveratrol have proven a considerable ability to stimulate Nrf2 signalling pathway and restore cellular defence against oxidation (71). Curcumin also blocks oxidative stress by controlling mitochondrial membrane stability and preventing lipid peroxidation. Resveratrol positively affects mitochondrial functioning and cell tolerance to oxidative stress by stimulating SIRT1 and AMPK pathways (72). Some studies claim that the overactivation of antioxidant signalling can negatively affect the

physiological processes of cell communication based on ROS production (73). As a result, due to the presence of ROS in physiological cellular signals, the suppression of oxidative signalling pathway is sometimes not therapeutic.

Mitochondrial dysfunction and reactive oxygen species generation

The mitochondria are among the principal sources of ROS formation inside cells and play key roles in the generation of ATP, maintenance of calcium balance and apoptosis regulation (74). Mitochondrial malfunction results in high ROS formation, inhibition of oxidative phosphorylation, decreased synthesis of ATP and stimulation of apoptosis processes. The plant phytochemicals help restore the proper functioning of mitochondria because of membrane stabilization, increased activity of the electron transport chain and mitochondrial biogenesis (75). One of the phytochemicals responsible for increasing mitochondrial biogenesis is resveratrol since it activates SIRT1 and PGC-1 α signalling pathways (76). The same protective action can be observed in the case of quercetin and catechin since they can protect mitochondrial DNA from oxidative stress and apoptosis induction.

Oxidative stress in neurodegeneration

The impact of oxidative stress on neuronal injury and neurodegenerative diseases is well-known (77). For instance, oxidative stress leads to the accumulation of amyloid beta plaques, hyperphosphorylation of tau protein and synaptic dysfunction in AD. Oxidative stress causes damage to dopamine neurons and enhances aggregation of alpha synuclein protein in PD (78).

Numerous phytochemical compounds exhibit antioxidant effects that can protect the neurons from oxidative stress. The antioxidant action of EGCG includes suppression of oxidative damage caused by iron and blocking neuronal apoptosis while curcumin prevents lipid peroxidation and inflammation in neural tissues (79).

Although there is sufficient experimental data regarding the potential of antioxidant therapy, its clinical effect remains controversial. Antioxidants were not found to be highly effective in treating neurodegenerative diseases in clinical practice since oxidative stress constitutes just one factor involved in neurodegenerative pathophysiology (80).

Limitations of antioxidant-based therapies

Although phytochemicals have been proven to have high antioxidant activity in the laboratory setting, there are several factors

Table 2. Crosstalk between oxidative stress, inflammation and neurodegeneration in chronic diseases

Pathological process	Key molecular events	Cellular consequences	Associated disorders	Phytochemical intervention
Oxidative stress	Excess ROS generation, lipid peroxidation	DNA damage, mitochondrial dysfunction	Diabetes, Alzheimer's disease	Nrf2 activation by curcumin and quercetin
Chronic inflammation	NF- κ B activation, cytokine release	Insulin resistance, neuronal injury	Obesity, Parkinson's disease	Suppression by resveratrol and EGCG
Mitochondrial dysfunction	Reduced ATP synthesis, impaired electron transport	Cellular apoptosis and metabolic failure	Neurodegeneration	SIRT1/AMPK activation by resveratrol
Neuroinflammation	Microglial activation and cytokine release	Synaptic dysfunction and neuronal loss	Alzheimer's disease	Curcumin-mediated inflammatory suppression
Protein aggregation	Amyloid-beta and α -synuclein accumulation	Progressive neuronal degeneration	AD and PD	Anti-aggregation effects of curcumin and EGCG

that limit their clinical applications. Poor bioavailability, rapid metabolism, lack of penetrance in tissues and variation in the compositions of phytochemicals have a substantial impact on treatment results (81). Moreover, some research studies have demonstrated that excessive amounts of antioxidants might have paradoxical pro-oxidant activity depending on the physiological state of the patient (82). Thus, further research should be concentrated on developing phytochemical delivery systems and establishing therapeutic concentrations for antioxidants.

Clinical translation and bioavailability challenges

Although there is plenty of evidence to prove the effectiveness of plant-based active ingredients, the translation of these agents into clinical practice is difficult due to numerous pharmacokinetic and pharmacodynamic issues (83). Many phytochemicals have shown great antioxidant and neuroprotective effects experimentally; however, these agents have exhibited inconsistent results in human clinical trials.

Poor bioavailability and pharmacokinetic limitations

One of the important challenges faced by plant-based therapeutics is that of poor oral bioavailability (84). A number of these bioactive compounds have poor aqueous solubility, poor intestinal absorption, rapid metabolism and extensive elimination from the body, which considerably diminishes their therapeutic value. One of the best-studied bioactive molecules subject to this problem of poor bioavailability is curcumin. Even though it shows great anti-inflammatory and neuroprotective effects under experimental conditions, curcumin has an extremely low concentration in the bloodstream upon oral administration, due to rapid intestinal metabolism and conjugation by the liver (85). Likewise, the rapid metabolism and poor systemic stability of resveratrol hinder its use for prolonged periods in treating diseases. Poor permeability across the blood-brain barrier also prevents the use of many plant-derived compounds in neurological diseases, even though some of them can have neuroprotective activity (86).

Variability in phytochemical composition

The other significant issue is the variation in phytochemical contents from different sources (87). The variations are greatly influenced by the environmental factors, the way plants are grown, harvested, extracted, stored and processed. This will result in discrepancies in the effectiveness of the phytochemicals in terms of their purity and compositions. There is thus a need for standardization of the extraction processes and dosing to ensure consistency across different experiments.

Piperine and bio enhancer controversies

Several bio enhancers, including piperine, have been thoroughly studied to enhance the absorption and systemic availability of phytochemicals (88). Piperine, a component of black pepper, has been found to increase curcumin bioavailability due to its interference with glucuronidation pathways in the liver and intestine. One such study revealed about 2000 % increase in curcumin bioavailability when used alongside piperine (89). On the other hand, further studies have revealed conflicting results as to the degree and reliability of such enhancement. The inconsistencies might arise due to variations in preparation methods and dosage of the agents employed in such experiments (90). Finally, safety concerns related to the use of bioenhancers, in terms of their interference with drug metabolism, have yet to be sufficiently addressed.

Contradictory clinical findings

Despite the significant therapeutic effects demonstrated by the phytochemicals in most preclinical studies, there have been some clinical trials that revealed inconclusive results (91). For instance, curcumin therapy used for treating patients with AD has revealed promising protective effects during experimentation but modest cognitive benefits when applied on patients (92). The other antioxidant phytochemicals have also demonstrated significant efficacy against some diseases in cellular and animal experiments but showed poor effects when tested in patients with severe diseases. Several factors such as different severities of the diseases, genetics of the patients, metabolism of patients, duration of treatment and formulations of the phytochemicals have been identified as key aspects determining their efficacy. Despite the significant results achieved in several preclinical experiments, phytochemicals still experience challenges in translating the effects into successful treatments. This paper highlights the variability of preclinical and clinical results in using phytochemicals as well as various factors that may explain the inconsistent effects. A comparison between various preclinical and clinical findings related to phytochemicals alongside their major translational challenges has been made in Table 3 below.

Safety concerns and long-term therapeutic use

While phytochemicals are considered generally safe due to their natural origin, studies regarding their long-term safety are not well-established for many substances (93). In some cases, high dosage of phytochemical supplements might cause adverse effects on the gastrointestinal system, liver or metabolism. Moreover, the excessive use of antioxidant supplements might affect physiological redox reactions and impair immune responses (94). Some phytochemicals have been identified as potential inhibitors of cytochrome P450 enzymes and may thus impact drug metabolism.

Further research should focus on long-term toxicological, pharmacological and clinical safety studies.

Strategies to improve clinical translation

Various methods have been developed in efforts to tackle problems that could arise in relation to the translation of phytochemicals into therapeutic drugs (95). Methods such as nano formulations, liposomes, phytosomes, polymer nanospheres and targeted drug delivery systems have been found to be very promising in resolving problems related to the stability and bioavailability of phytochemical drugs. Personalized nutrition using genomics and microbiomics can also be used to enhance individual therapy.

Nanotechnology and advanced delivery systems for phytochemical therapeutics

However, nanotechnology-driven drug delivery systems have proved highly effective in addressing the various pharmacokinetic hurdles that are posed using plant-derived bioactive agents (96). The inefficiencies of many of the phytochemicals can be attributed to poor solubility in water, fast metabolic breakdown, inadequate GI absorption and difficulty penetrating the blood-brain barrier. Fig. 3 presents advanced nano-delivery systems designed to overcome the pharmacokinetic limitations of phytochemicals.

Nano formulations and improved bioavailability

The therapeutic benefits can be increased by using nano formulations through an increase in the surface area, improving their solubility, reducing degradation of the active ingredient and

Table 3. Comparative analysis of experimental and clinical outcomes of major phytochemicals

Emerging strategy	Mechanistic basis	Therapeutic advantages	Current challenges	Future Potential
Nano-phytotherapeutics	Nanocarrier-mediated delivery	Improved bioavailability and BBB penetration	Nanotoxicity and formulation stability	High translational potential
Precision nutrition	Individualized metabolic profiling	Personalized therapeutic responses	Complex biomarker integration	Precision medicine applications
AI-assisted phytochemical screening	Computational target prediction	Rapid identification of bioactive compounds	Need for experimental validation	Accelerated drug discovery
Multi-omics integration	Genomics, proteomics, metabolomics	Comprehensive pathway analysis	Large-scale data interpretation	Systems pharmacology
Combination phytotherapy	Multi-compound synergistic action	Enhanced therapeutic efficacy	Herb–drug interaction risk	Chronic disease management
Microbiota-targeted therapy	Gut microbial modulation	Improved metabolic and neurological health	Interindividual microbiome variability	Gut–brain therapeutic modulation

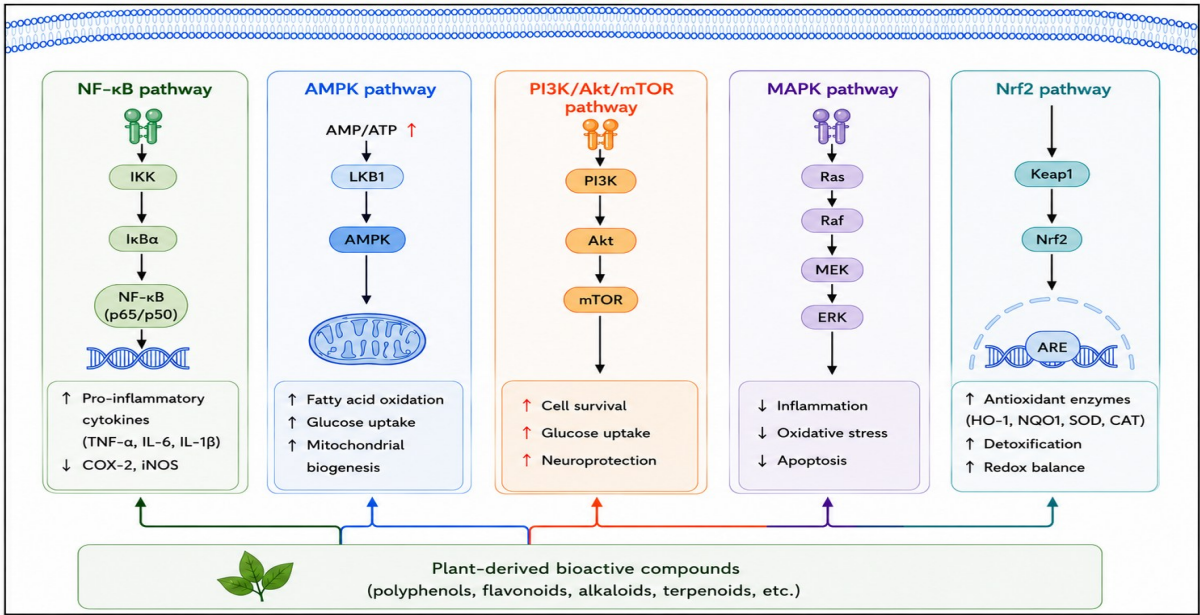


Fig. 3. Molecular signalling pathways targeted by plant-derived bioactive compounds. Phytochemicals such as polyphenols, flavonoids, alkaloids and terpenoids modulate key intracellular pathways, including nuclear factor kappa B (NF-κB), AMP-activated protein kinase (AMPK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK) and nuclear factor erythroid 2-related factor 2 (Nrf2). Regulation of these pathways results in reduced inflammation, enhanced antioxidant defence, improved metabolic homeostasis and increased cellular survival. The interconnected crosstalk among these signalling networks highlights the multi-target therapeutic potential of plant-derived bioactives in metabolic and neurodegenerative diseases.

promoting cellular uptake (97). Different forms of nanocarrier formulations such as liposomes, polymeric nanoparticles, nano emulsions, solid lipid nanoparticles, dendrimers and phytosomes have shown promising potential for the delivery of phytochemicals.

For instance, nano-curcumin formulations show greater stability and increased therapeutic activity compared to the conventional formulations of curcumin (98). The nano-curcumin formulations also show better brain-barrier penetrability, which improves its neuroprotective potential against neurodegenerative disorders.

Similarly, nano carrier formulation of resveratrol shows pharmacokinetic stability along with prolongation of systemic circulation time. Nano carrier encapsulation of EGCG and quercetin improves their antioxidant and anti-inflammatory properties.

Liposomes and phytosomes

Liposomes are vesicles made up of phospholipids that can encapsulate hydrophilic and hydrophobic phytochemicals (99). They help to enhance stability, minimize drug degradation and ensure tissue-specific drug delivery. The Phytosome approach uses

complexes formed by phytochemicals and phospholipids, which makes their transport through membranes more effective and increases their absorption (100). Various formulations using curcumin and quercetin as phytosomes have proved better bioavailability than traditional extract forms. Nevertheless, major issues like large scale production, instability in formulations and high cost remain.

Polymeric nanoparticles and controlled drug release

Controlled and sustained release of phytochemicals is possible due to the use of polymeric nano particles and hence therapeutic effectiveness is increased along with the reduction in dosing frequency (101). Polymers that degrade are commonly employed because of their biocompatibility and controlled release properties. The other advantage of using polymeric nanoparticles is protection against degradation through metabolism and increased effectiveness of tissue targeting. Studies have shown higher efficacy of anti-inflammatory and neuroprotective properties when polymeric nanoparticles containing phytochemicals were tested in contrast to free phytochemicals (102).

Nanotechnology in neurodegenerative disorders

Targeting therapeutic agents to the brain continues to be quite difficult due to the selective characteristics of the blood-brain barrier (103). Nano particles offer great promise in terms of enhancing the delivery of phytotherapeutics for neurological purposes. Nano-curcumin has proven to confer superior cognitive protection and decrease amyloid-beta deposition in experimental models of AD (104). Likewise, the use of resveratrol-loaded nanoparticles has increased neuronal uptake as well as mitochondrial protection in experimental models of PD. Some types of nano particles also allow for specific targeting to inflammatory neurons to minimize side effects. There is still little knowledge regarding possible neurotoxicity due to nano particle accumulation.

Challenges and limitations of nanotechnology-based approaches

Despite significant therapeutic potential shown by phytochemical delivery systems based on nanotechnology, there are still some issues to be addressed (105). Scale-up, formulation stability, reproducibility, storage conditions and costs of nanoparticle fabrication still prevent their application in medicine. The problem of toxicity related to nano scale particles also should not be underestimated. Some nano materials can cause oxidative stress, inflammation or accumulation in tissues under prolonged usage (106). The process of regulatory approval of nano medicines also is a challenging issue due to insufficient safety information about them.

Future perspectives in nano-phytotherapeutics

The future work needs to emphasize the development of multifunctional nanoparticles that can facilitate targeted delivery, drug release, increased permeability across the blood-brain barrier and improved pharmacokinetic stability (107). The application of nanotechnology in conjunction with the use of precision medicine, artificial intelligence-enabled drug design and systems biology might optimize phytotherapeutic drugs as well. Phytotherapy along with other pharmacotherapies will be an important consideration to achieve desired therapeutic effect and reduce adverse effects.

Gut-brain-metabolism axis and phytochemical interactions

The gut-brain axis is an intricate bidirectional system that connects the gut, the central nervous system, the immune system and metabolism (108). It has increasingly become clear that gut microbiota is essential for controlling metabolism, inflammation, neuronal activity and cognitive processes. Disruption in the composition of gut microbiota, known as dysbiosis, has been linked with obesity, diabetes, chronic inflammation and neurodegenerative conditions (109). Bioactive components of plants have a considerable impact on the composition and metabolism of gut microbiota, hence having implications for systemic metabolism and neurological functions. At the same time, the gut microbiota regulates the metabolism and efficacy of phytochemicals.

Gut microbiota and metabolic dysfunction

Intestinal microorganisms play a crucial role in nutrient metabolism, energy balance and immunological regulation (110). Imbalance of bacterial flora and population can result in intestinal mucosal dysfunction, endotoxin formation and chronic systemic inflammation. Dysbiosis-mediated increased concentrations of LPS have been implicated in metabolic endotoxemia and NF- κ B and TLR4-dependent signalling pathways (111). Such an inflammatory state leads to the induction of insulin resistance and fat cells malfunctioning associated with metabolic problems. Several

phytonutrients act as prebiotics, stimulating favorable bacteria like *Lactobacillus* and *Bifidobacterium* (112). Polyphenols also increase SCFA content, which comprises of butyrate, acetate and propionate.

Gut-Brain Communication and Neuroinflammation

Several pieces of evidence point toward gut microbiota influencing brain functions via neural, hormonal, metabolic and immune mechanisms (113). Gut microbiota metabolites, inflammatory mediators, neurotransmitters and vagus nerve activity play crucial roles in gut-brain axis communication. Any disturbance in gut microbiota composition can increase gut wall permeability, resulting in the movement of inflammatory mediators into the bloodstream (114). Inflammatory mediators, in turn, can enter the brain and cause microglial activation, neuroinflammation and neuron impairment. There is evidence pointing toward gut microbiota dysbiosis involvement in neurodegenerative diseases like Alzheimer's and Parkinson's diseases by increasing oxidative stress and inflammation and disturbing neurotransmitter metabolism (115).

Phytochemicals and gut microbial modulation

Phytochemicals from plants have been shown to considerably affect the population and metabolism of microbes present in the gut (116). The presence of polyphenols, flavonoids and fibres in food encourages microbial growth and suppresses pathogenic bacteria. Curcumin is known to restore microbiota diversity and decrease gut inflammation caused by metabolic diseases (117). Resveratrol has been found to modify the composition of gut microbiota as well as suppress endotoxemia and inflammation by reducing harmful bacteria. Quercetin and catechins are known to not only enhance gut integrity but also suppress inflammation through reduction of oxidative stress in the gut. Based on these observations, it can be concluded that modification of gut microbiota is an important factor contributing to the health benefits of phytochemicals. However, the relationship between phytochemicals and gut microbiota remains extremely complicated.

Short-chain fatty acids and neuroprotection

Short-chain fatty acids resulting from microbial fermentation possess anti-inflammatory, metabolic and neuroprotective effects (118). Notably, butyrate improves gut-barrier function, downregulates inflammatory mediators and modulates neurological processes. Some phytochemicals exert indirect effects on the production of SCFAs by activating beneficial microbial communities. The presence of elevated levels of SCFAs ultimately results in enhanced insulin sensitivity, decreased oxidative stress and reduced neuroinflammation.

Recent findings further indicate that SCFAs can modulate blood-brain barrier permeability and neuronal energy metabolism.

Challenges and future directions

While the gut-brain-metabolism axis is implicated in chronic diseases based on considerable scientific data, some aspects are not yet fully understood (119). The complex dynamics of interactions among phytochemicals, microflora, host metabolism and immune response depend upon many factors, including diet, genetics, age, environment and disease state. Currently, there is still a paucity of clinical information about phytochemical treatments aimed at modulating microbiota functions and no treatment protocols have been established yet. Also, due to individual differences in microflora, predicting an effect is quite challenging. Thus, future studies should address the need for combined use of microbiome

analysis, metabolomics, personalized nutrition and systems biology methods to better understand the relationship between phytochemicals and gut microbiota.

Future perspectives and emerging therapeutic strategies

Phytochemicals from plants are continuing to receive great attention from scientists due to their potential multi-target treatment approach toward metabolic and neurodegenerative diseases (120). However, the clinical success of these bioactive compounds needs further mechanistic insights, pharmacokinetics improvements and individualization of therapeutic regimens. Future studies should be oriented towards the development of phytotherapeutics based on molecular biology, systems pharmacology, nanotechnology, artificial intelligence and precision medicine. Recent developments in nanotechnology, systems biology, artificial intelligence, precision nutrition and microbiota investigations opened great possibilities for improvement of phytochemical-based therapies. Emerging methods seek to address major challenges in clinical trials such as insufficient bioavailability, non-uniform response to therapy and lack of sufficient target-specificity. Major advanced therapeutic approaches and their applications in the future are provided in Table 4.

Precision nutrition and personalized therapeutics

Inter-individual variation plays an important role in determining the outcome of treatment involving phytochemicals (121). Genetic differences, the metabolic state, the composition of the gut microbiome, age, diet and the environment all play a role in the effectiveness of the phytochemicals. The application of precision nutrition using genomics, metabolomics and microbiome studies is likely to provide individualized approaches to therapy (122). Individualized therapy with phytochemicals might help in determining optimal doses, increase efficacy and reduce side effects.

Artificial intelligence and computational drug discovery

The application of AI and computational modelling for phytochemical screening, target identification and interaction predictions is rapidly gaining popularity (123). The machine learning models can study the molecular data and screen phytochemicals with therapeutic efficacy against metabolic and neurodegenerative pathways. Further, using computational docking and network pharmacology, multi-target interactions of phytochemicals with cell signalling pathways can be studied (124). These methods can help to identify the optimized combination of phytochemicals, as well as understand their therapeutic actions. Thus, the integration of

AI-based phytochemical screening with experimental validations can significantly improve the drug discovery process.

Multi-omics and systems biology approaches

Metabolic and neurodegenerative diseases consist of highly complex molecular networks and thus cannot be comprehensively addressed using a single target analysis approach (125). Genomics, transcriptomics, proteomics, metabolomics and microbiomics constitute multi-omics methods that can help in comprehensively characterizing molecular interactions associated with the diseases. The use of systems biology approaches could possibly contribute to identification of key molecular pathways affected by phytochemicals and elucidating their differential effects on therapy (126). Such integration of omics and phytochemicals could lead to more specific therapeutic strategies.

Moreover, biomarker-based monitoring could enhance assessment of effectiveness of phytochemicals in clinical trials.

Combination therapies and synergistic interactions

The use of a combination therapy involving a variety of phytochemicals or the combination of phytochemicals with pharmacological drugs can be more effective than monotherapies (127). The interaction between different bioactive substances might lead to increased antioxidative action, regulation of inflammation processes, mitochondrial health and neuronal activity. For instance, a simultaneous application of curcumin and piperine will result in better bioavailability and a combination of polyphenols is likely to have complimentary anti-inflammatory and neuroprotective properties (128). At the same time, there is still a need for more studies to address safety issues regarding possible herb-drug interactions.

Standardization and Clinical Validation

Inconsistency in formulations used and differences in the methodology of experimentation pose great challenges in translating phytochemical drugs into the clinical field (129). Differences in the methodology used can make it difficult to compare results from clinical studies and those from experimental research. In future research, emphasis should be put on conducting larger randomized controlled clinical trials that use consistent formulations. It will also be necessary to consider pharmacokinetics, quality controls and long-term testing for safety. There is need for regulatory policies that specifically address phytochemistry and nano-phytomedicines.

Table 4. Emerging advanced therapeutic strategies for phytochemical-based interventions

Emerging strategy	Mechanistic basis	Therapeutic advantages	Current challenges	Future potential
Nano-phytotherapeutics	Nanocarrier-mediated delivery	Improved bioavailability and BBB penetration	Nanotoxicity and formulation stability	High translational potential
Precision nutrition	Individualized metabolic profiling	Personalized therapeutic responses	Complex biomarker integration	Precision medicine applications
AI-assisted phytochemical screening	Computational target prediction	Rapid identification of bioactive compounds	Need for experimental validation	Accelerated drug discovery
Multi-omics integration	Genomics, proteomics, metabolomics	Comprehensive pathway analysis	Large-scale data interpretation	Systems pharmacology
Combination phytotherapy	Multi-compound synergistic action	Enhanced therapeutic efficacy	Herb-drug interaction risk	Chronic disease management
Microbiota-targeted therapy	Gut microbial modulation	Improved metabolic and neurological health	Interindividual microbiome variability	Gut-brain therapeutic modulation

Conclusion

Plant-based bioactive components have considerable medicinal value in the management of metabolic disorders, chronic inflammation, oxidative stress and neurodegeneration via the regulation of several interconnected molecular pathways. Such phytochemicals, which include curcumin, resveratrol, quercetin, epigallocatechin gallate and berberine, impact various signalling pathways, such as NF- κ B, AMP-activated protein kinase (AMPK), PI3K/Akt, MAPK, Nrf2 and SIRT1.

Pleiotropy is among the significant advantages associated with phytochemicals in the treatment of complex chronic conditions where multifactorial pathogenic mechanisms are at play. Besides their potential for molecular regulation, phytochemicals have been found capable of altering the composition of gut microbiota, mitochondrial physiology and energy metabolism within cells, thereby adding to their relevance as potential therapeutic agents. Nonetheless, despite considerable preclinical data, there have not been many cases where their potential has been translated into practice due to poor bioavailability, pharmacodynamic instability, inconsistent clinical outcomes, variations in phytochemical profile and lack of large randomized human studies. Indeed, it is important to mention that there are certain controversial findings and dose-related effects in some studies which require a more realistic and objective approach towards the possible application of phytochemicals rather than exaggerated assertions about their effectiveness. However, advances made in disciplines like nanomedicine, precision nutrition, systems biology, artificial intelligence-based drug discovery and personalized medicine can be helpful in addressing current translational problems. In general, the use of phytochemical therapeutics together with nanotechnology, precision medicine, systems biology and artificial intelligence can be helpful in developing new multi-target therapies for complicated diseases.

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Authors' contributions

KR was responsible for conceptualization, literature collection and preparation of the original draft. SR contributed to conceptualization, supervised the work and was involved in reviewing and editing the manuscript. All authors have read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this review article.

Ethical issues: None

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