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Berberine in metabolic and neurodegenerative disease: Functional food potential and therapeutic implications

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ABSTRACT

Background: Alzheimer's disease (AD) and metabolic issues such as type 2 diabetes mellitus (T2DM) represent growing public health burdens, with current treatments often providing only symptomatic relief or carrying significant side effects. Berberine, a plant-derived isoquinoline alkaloid, has been investigated for its dual roles in metabolic regulation and neuroprotection. Its antioxidant, anti-inflammatory, and metabolic effects suggest promise in addressing both disease classes simultaneously.

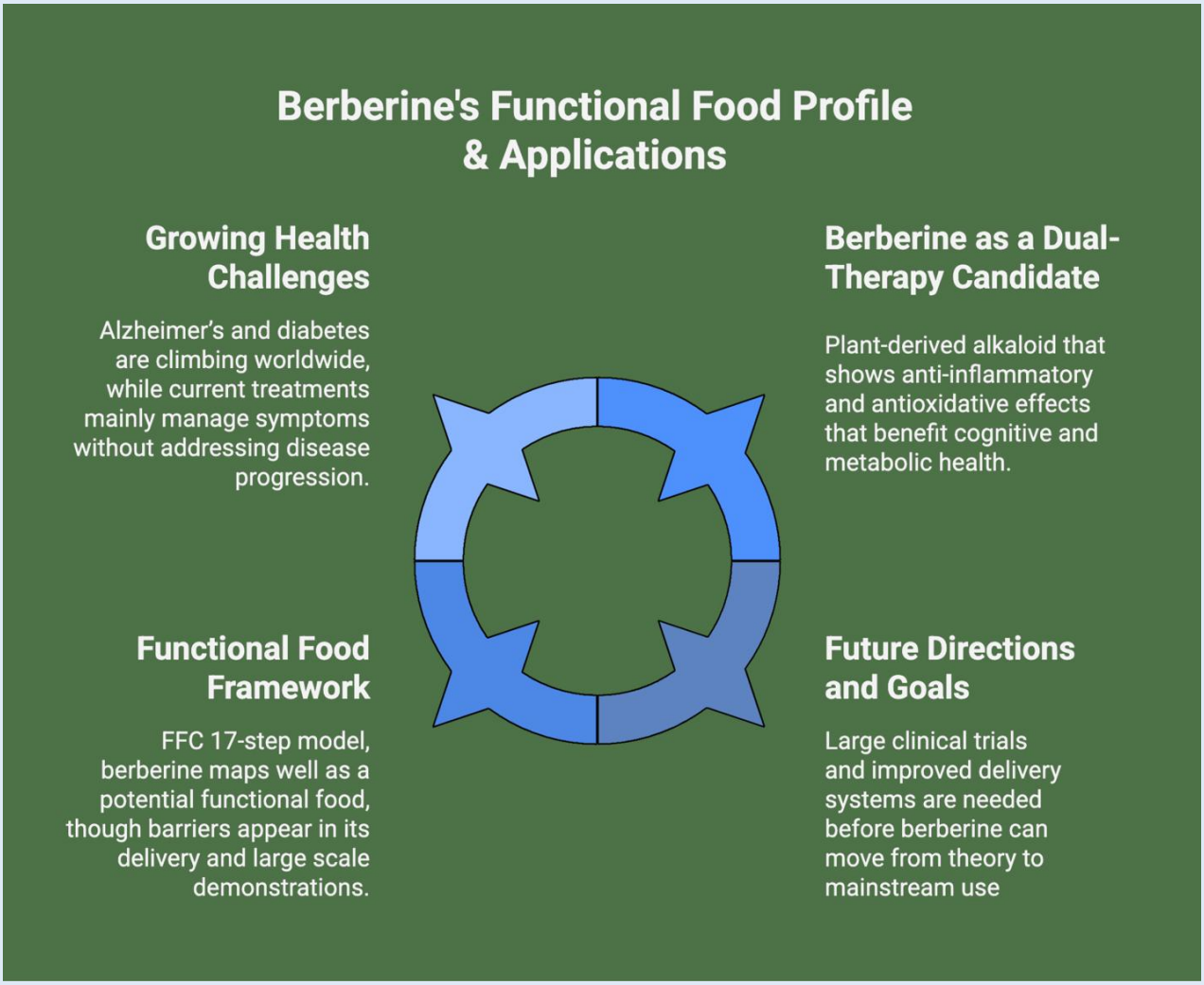
Objective: This review synthesizes the evidence for berberine in both AD and T2DM therapy, evaluates its drug performance using 15 key parameters, and examines its practical advantages and limitations. The aim is to assess its therapeutic potential through the Functional Food Center's 17-parameter framework.

Methods: A literature review was conducted using PubMed, Scopus, and FFHDJ.com databases using combinations of keywords: "berberine," "Alzheimer's," "dementia," "type 2 diabetes mellitus," "dyslipidemia," "metabolic disease," and "clinical trials." Priority was given to recent (2000–2025) systematic reviews, meta-analyses, and randomized controlled trials.

Results: Preclinical studies consistently demonstrate that berberine improves cognitive function, reduces amyloid-beta and tau pathology, and attenuates oxidative stress and neuroinflammation. Clinical trials in type 2 diabetes patients report significant improvements in glycemic control, HbA1c levels, and lipid profiles. Despite its low oral bioavailability, advances in delivery formulations show promise for enhancing clinical translation.

Conclusion: Berberine demonstrates broad potential as a functional food with applications in both metabolic and neurodegenerative care. Its dual effects suggest it may bridge preventive and therapeutic domains, although robust clinical trials, particularly in dementia, remain lacking. Future research should address bioavailability challenges and evaluate berberine in larger, diverse patient populations.

Keywords: berberine, Alzheimer's disease, type 2 diabetes mellitus, functional foods, nutraceuticals



INTRODUCTION

Alzheimer's disease (AD) makes up an estimated 60-80% of dementia cases, making it the most common cause of dementia [1]. Existing treatments like cholinesterase inhibitors (donepezil) and NMDA antagonists alleviate symptoms, but they fail to pause or reverse AD progression [2]. Most interventions provide limited benefits in advanced stages and can pose adverse effects.

Type 2 diabetes mellitus (T2DM) makes up around 90-95% of the 38 million diabetes cases in the United States and is a major contributor to morbidity and cardiovascular disease [3]. Current treatments like statins and fibrates can effectively manage blood glucose and lipid levels, but they can often carry adverse effects and do not address the varied nature of these conditions [4,5].

T2DM is increasingly recognized as a risk factor for AD, with insulin resistance serving as a key link between the two diseases. Chronic metabolic dysfunction in T2DM promotes oxidative stress, disrupts neuronal signaling pathways, and favors the buildup of amyloid-β and hyperphosphorylated tau, which contributes to the onset and progression of AD [6]. Therefore, there exists a desire for interventions that target both metabolic and neurodegenerative pathways. Nutraceuticals, as defined by the Dietary Supplements and Nutraceuticals Journal, are "foods, or parts of food, such as isolated nutrients, food supplements, herbal products, extracts, and processed food products, that provide health benefits to individuals and can aid in the prevention and treatment of diseases."[7] Berberine is one such candidate, extracted from plants such as Berberis vulgaris, that holds a variety of effects. Over the past two decades, with its history in traditional medicine, berberine's capabilities as an antioxidant, anti-inflammatory, metabolic enhancer, and neuroprotective agent have all prompted further investigation into its feasibility as a dual-domain therapeutic [8,9].

This paper explores the proposition that berberine fits the functional food model provided by the Functional Food Center (FFC) for the prevention and management of AD and metabolic diseases. This will be done by applying a 17-parameter framework to systematically assess berberine's pharmacological and practical profile.

METHODS

A literature review was conducted using PubMed, Scopus, and FFHDJ.com databases using combinations of keywords: "berberine," "Alzheimer's," "dementia," "type 2 diabetes mellitus," "dyslipidemia," "metabolic disease," and "clinical trials." Priority was given to recent (2000–2025) systematic reviews, meta-analyses, and randomized controlled trials. The review focused on evidence for berberine's efficacy, safety, clinical applications, and delivery systems.

RESULTS

15-Parameter Evaluation of Berberine: In line with the Dietary and Supplements and Nutraceuticals Journal's definition for nutraceuticals, 15 parameters were selected to determine berberine's practicality and pharmacological effects based on a similar analysis of metformin [10]. Together, these parameters seek to demonstrate berberine's potential as both a dietary supplement and therapeutic agent. By applying these criteria, researchers can better understand where berberine stands in the range between natural remedies and clinically-applied medicines.

1. Side Effects: Berberine is tolerated well at standard doses and has shown low toxicity and minimal side effects in animal studies. The most common issues associated with its use are transient gastrointestinal symptoms such as diarrhea, constipation, and abdominal discomfort [11,12]. No severe side effects have been consistently associated with berberine use at therapeutic doses, although risks of toxicity are higher when using injection versus oral methods of administration [13].
2. Contraindications: Because berberine is cleared by the liver and excreted via bile along with feces and urine, contraindications could include severe hepatic or renal impairment [11].
3. Route of Administration: Berberine is typically administered orally, but due to its low bioavailability, various other methods of administration are being explored. However, some methods like intravenous delivery have concerns for serious side effects (drop in blood pressure, respiratory arrest), so most clinical trials opt for oral administration [12,14-15].
4. Half-life: Pharmacokinetics studies of berberine report a range of half-life values depending on dosage size and method. Early studies suggest a short half-life, particularly after oral dosing.[16] However, more recent studies in both animal and

human subjects indicate that berberine has a relatively longer half-life at around 20 hours [14,17].

5. Pharmacokinetics: After oral administration, berberine reaches its highest tissue concentrations in the liver, followed by the kidneys [18]. It then goes through rapid phase I and II metabolism in the liver and intestinal wall, resulting in a range of metabolites. It is finally excreted from the body mostly through feces but also less in urine, however research has shown it to be dependent on pathological conditions [11,19].
6. Drug Interactions: Berberine could enhance the effect of hypoglycemic agents, antihypertensives, and anticoagulants [20]. Patients using these drugs physiologic tolerance or dependence has been reported for berberine.
7. Cost and Accessibility: Berberine is inexpensive and available over the counter in many countries as a dietary supplement. It can be produced at scale from multiple plant sources, which makes it an accessible option for widespread use [21].
8. Indications: The medical conditions or diseases for which berberine is prescribed, which traditionally have been gastrointestinal and metabolic disorders [22]. However, recent preclinical studies and reviews highlight indications for neuroprotection, AD, Parkinson's disease, stroke, and psychiatric disorders [23].
9. Efficacy vs. Safety: Preclinical studies consistently show efficacy in improving cognitive deficits, reducing amyloid and tau pathology, suppressing oxidative stress and microglial activation, and improving synaptic function [24]. In clinical trials, T2DM patients experienced a significant improvement in glycemic control and HbA1c levels. A randomized clinical trial on 113 participants with T2DM resulted in siginificantly lower hemoglobin A1c levels after 12 weeks of berberine ursodeoxycholate [25], while another phase 2 trial of 100 people saw a significantly greater reduction in liver fat content after use of berberine ursodeoxycholate [26]. Berberine's safety has been regularly proven at tested doses and demonstrates a wide therapeutic window [27].
10. Patient Demographics: Most clinical research focuses on adults with metabolic disease with a particular focus on T2DM. Participants are mostly healthy aside from their primary metabolic condition, which may limit generalizability to more complex patient populations. Elderly patients, particularly those with AD or multiple comorbidities, are underrepresented in clinical studies.
11. Bioavailability: One of berberine's main weak points is its exceptionally low oral bioavailability (<1%) due to poor intestinal absorption [28]. Advances in formulation (nanoparticles, liposomes) to overcome this weak point show promise but remain experimental [23]. Clinical translation of these technologies is required.
12. Therapeutic Index: Berberine's therapeutic index is broad, with toxicity at doses much higher than recommended dietary or supplement intake [27].
13. Drug and Food Interactions: Currently, there is little evidence for foods that necessitate strong avoidance when taking berberine.
14. Adherence/Compliance: As a supplement, compliance is subject to patient motivation. Daily, multiple-dose regimens and possible GI upset may affect adherence. Improved formulations (fewer doses, better tolerability) could enhance compliance.

DISCUSSION

Berberine Within Functional Food Science: Berberine belongs to a growing group of functional foods that are increasingly linked to preventive health strategies, particularly in their role of diabetes management [29]. The FFC defines functional foods as "Natural or processed foods that contain biologically-active compounds; which, in defined, effective, non-toxic amounts, provide a

clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms."[30] Although berberine is more commonly thought of as a drug supplement rather than a typical food, its properties align with the FFC's conceptual structure of a functional food where bioactive compounds are evaluated for their relevant health benefits. Similar studies, such as analyzing Acacia bark-derived proanthocyanidins' role in visceral fat loss, comparably place derivative compounds in the role of a functional food, based on their effects on the participants' health [31]. In this context, berberine's antioxidant and anti-inflammatory mechanisms correspond to measured biomarker outcomes (reductions in oxidative stress and improvement in glycemic control).

It is important to acknowledge that the FFC, although it allows processed foods, does not consider pills or capsules as part of its "food" definition [32]. Instead, food is defined as being a component of a normal diet for optimized nutrition. This distinction emphasizes the FFC's values in incorporating beneficial bioactive compounds that may not initially be considered "food" into regular diets as a frontline preventative measure rather than reserving them for clinical medications [33]. A comparable study analyzing eucalyptus leaf extract containing oenothein B was evaluated in a 12-week randomized, double-blind trial with 198 subjects [34]. Administration of the powdered eucalyptus leaf extract at 3.38mg equivalent of oenothein B per day resulted in significantly reduced visceral fat area, waist circumference, and BMI in healthy adults consuming fructose-rich diets. This integration of bioactive compounds into daily diets that don't restrict them to pharmaceuticals can thus produce measurable health benefits consistent with the FFC's functional food philosophy. By presenting berberine not simply as a drug but as a supplement that can be included with regular foods, it may improve accessibility and long-term use. The nature of functional foods, being long-term consumption, aligns with the gradual progression of chronic diseases [35]. For example, a study analyzing the extended administration (12 weeks) of a highly bioavailable formulation of curcumin (TS-P1) in healthy adults established long-term safety for the bioactive compound through daily dietary intake [36]. This reinforces the ability of bioactive compounds like berberine and curcumin to play a more dietary role than solely a medication. In such a manner, the functional food model shifts the focus of bioactive compounds like berberine from treating symptoms after onset to preventing their emergence through dietary intervention. However, functional foods and their bioactive compounds in general have not been limited to the preventative space, as many are investigated as adjunctive interventions in populations already experiencing metabolic conditions. A recent study examining the effects of a dietary compound tablet containing cinnamon, chromium, mulberry leaf, zinc, and selenium on hyperglycemic mouse found a significant decrease in fasting blood glucose levels for medium (133.34 mg/kg) and high (400 mg/kg) doses (18.3% and 24.7% respectively), demonstrating the bioactive compound's potential in an adjunctive treatment [37]. Overall, framing berberine through the lens of functional food science expands its potential to contribute to chronic disease management and shifts its role from only a medical supplement to a bioactive component of the daily diet.

15. should be monitored and have their dosages adjusted in conjunction with berberine.
16. Tolerance and Dependence: No evidence of

Functional Food Center (FFC) Framework Analysis: For introducing these functional foods into public markets, the FFC establishes a 17-step framework that guides the evaluation and eventual recognition of functional foods through assessments of bioactivity, efficacy, safety, pharmacokinetics, epidemiology, and market potential [38].

Table 1. FFC's 17-step framework for inducting a functional food.

Step Number	Description of Steps to Create Functional Food Products
1	Establishes a goal of the functional food product
2	Determines relevant bioactive compound(s)
3	Establishes the appropriate dosage of bioactive compound(s)
4	Establishes the appropriate time of consumption of bioactive compound(s)
5	Determines the specific pathway and mechanism of action
6	Establishes relevant biomarker(s)
7	Chooses an appropriate food vehicle for bioactive compound(s)
8	Provides preclinical studies on efficacy and safety
9	Provides clinical trials for dosage, efficacy, and safety
10	Creates a special label that informs consumers of the most effective way to consume the product
11	Publications are submitted to peer-reviewed journals, preferably in open access
12	Educates the general public
13	Sends information to credible governmental agencies, such as the FDA, for approval
14	Official establishment of the accredited functional food product
15	Release the functional food product to the market (Receive the basic category [level C])
16	Provides epidemiological studies (Reapply for the approval for a new category [level B])
17	Provides after-market research. (Reapply for the approval for a new category [level A]).

Berberine's potential as a functional food begins with two therapeutic goals, primarily as a treatment for metabolic diseases, mainly T2DM, and secondarily addressing neurodegeneration and cognitive decline associated with AD (Step 1). The active compound responsible for these effects is berberine itself, as a bioactive alkaloid derived primarily from plants such as *Rhizoma coptidis* and *Berberis* species (Step 2). Dosages for trials typically range between 500 and 1,500 mg daily, [12,39] but further research is necessary to determine a dosage size and timing that has an optimal impact on the nervous system and metabolic regulation (Step 3, 4). In order to exhibit its antioxidative, anti-inflammatory, and metabolic effects, berberine operates through multiple biological pathways. Studies have found that berberine increases superoxide dismutase, an antioxidant enzyme that catalyzes the conversion of superoxide radicals, which play an essential role in reducing oxidative stress.[40] The alkaloid activates the AMP-activated protein kinase (AMPK) pathway, which enhances glucose uptake and improves insulin sensitivity [41]. Additional mechanisms include increasing glucagon-like peptide-1 secretion and suppressing pro-inflammatory signaling, all of which contribute to improving glycemic control and lipid metabolism [42]. By selectively inhibiting protein expression (gp91phox), berberine restores cellular redox balance and reduces superoxide production in macrophages [43] while enhancing antioxidant enzyme activities [44]. These actions mitigate oxidative-stress-induced cytotoxicity and brain injury (Step 5). In assessing berberine's efficacy, biomarkers such as retention in synaptic density [45] and reduction in Aβ levels [46] have been identified as indicators for its neuroprotective potential. Berberine administration has also been shown to significantly reduce the content of several lipid biomarkers, including CE (16:1), HexCer (D18:1/19:0), and PE(P-20:0_18:1) (Step 6) [47].

Since berberine is not typically consumed significantly in food and is instead obtained as an extract from plant matter, Step 7 is not directly applicable. However, due to its poor oral bioavailability [39], efforts to explore different delivery vehicles have yielded developments in nanoparticle [48] and hydrogel-based formulations [49]. Although there is substantial data for

berberine's efficacy and safety in preclinical models [44] (Step 8), there is a lack of large-scale, phase 3 clinical trials, especially targeting AD patients. In comparison, larger clinical trials (n >= 100) have been primarily based on T2DM [26,50,51] and psychiatric disorders [52] (Step 9). Due to its lack of a food vehicle, as mentioned in Step 7, there is a notable gap in consumer-directed communication, although specialized labeling for optimal dosage will be easier to obtain after more effective and defined pathways to delivery are established (Step 10). Nonetheless, abundant peer-reviewed publications bolster the scientific credibility and transparency surrounding berberine (Step 11).

Steps 12 through 17 remain largely unattainable at this stage due to the incomplete progression of earlier steps. Without a tested, viable delivery method and large-scale trials demonstrating both efficacy and safety in addressing both metabolic and neurodegenerative conditions, public education campaigns shouldn't take place to avoid the risk of spreading misleading health claims (Step 12). The lack of large-scale clinical data is also an obstacle to Step 13, since submission to governmental agencies like the FDA for approval (Step 13) requires robust clinical data demonstrating the compound's effectiveness. Unlike compounds such as curcumin that have been under GRAS review multiple times, berberine lacks an established regulatory pathway as a functional food. Its poor bioavailability further complicates approval compared to compounds that have recognized delivery formulations. Similarly, Steps 14 to 17 cannot be completed without establishing prior foundations. Overall, berberine meets several key criteria that currently map it to the early to mid-stages of the FFC 17-step framework.

Table 2. Comparing berberine's roles in metabolic and neurodegenerative disorders.

Category	Reported Effects	Key Mechanisms
Metabolic Disorders (T2DM, hyperlipidemia, metabolic syndrome)	• Lowers fasting blood glucose and HbA1c [37] • Improves insulin sensitivity [41]	• AMPK activation [41] • Lipid-lowering activity [47]
Neurodegenerative Disorders (AD, dementia)	• Reduces amyloid-beta aggregation and improves synaptic [24, 46] • Attenuates oxidative stress and neuroinflammation [24, 40]	• Inhibition of amyloid-beta aggregation [46] • Reduction of tau hyperphosphorylation [24]

Future Directions: The most immediate challenge is determining whether the neuroprotective capabilities of berberine observed in animal models [53–56] translate to human populations. While phase 2 trials focused on T2DM have shown promising results in relatively larger human populations, like lowering glycated hemoglobin [51], the optimization of dosage sizing, delivery methods, and timing will be necessary to translate the anti-inflammatory neuroprotective effects seen in animal testing. Further advances in nanoparticle or other delivery systems will also be necessary, since berberine's notably low bioavailability will be a substantial obstacle to establishing its real-world practicality.

Progress depends on the execution of more large, well-designed Phase II and III randomized controlled trials that evaluate efficacy, safety, and dosing for individuals diagnosed with AD and T2DM across diverse populations and disease stages. Additionally, comparative trials with existing neurodegenerative therapies, for example donepezil or memantine, should be conducted to determine berberine's role as a viable, competitive alternative treatment. Addressing these gaps will be essential to move berberine from theoretical to a clinically validated and widely accessible intervention.

Novelty: This study's novelty lies in its comprehensive evaluation of berberine as a potential functional food for AD and metabolic disorders. It uniquely applies a 17-parameter framework from the Functional Food Center to systematically assess berberine's pharmacological and practical profile, synthesizing evidence for its use in AD and type 2 diabetes mellitus therapy. The research also highlights berberine's antioxidative, anti-inflammatory, and metabolic effects, mapping its development pathway as a functional food using the FFC framework.

Practical Implications: This study provides a structured approach to evaluating the potential of natural compounds like berberine for addressing complex health issues such as AD and T2DM, and helps guide future research in validating functional food candidates that may provide alternative treatments to chronic diseases. The exploration and integration of functional foods could reduce the reliance on modern treatments that may fail to target underlying disease progression, are too expensive for frequent usage, or are accompanied by undesirable side effects. This mini-review highlights berberine's potential as an accessible dietary supplement that supports cognitive and metabolic health and its therapeutic implications against chronic diseases like T2DM and AD.

CONCLUSION

Berberine embodies many characteristics that define a functional food for metabolic and neurodegenerative diseases. Preclinical evidence reveals that administration of berberine is safe and multi-targeted in its effects, but is greatly hampered by its lacking bioavailability. By suppressing core pathological features, animal models support its neuroprotective efficacy in mitigating AD. However, practical implementation is mainly constrained by low bioavailability, and the limited large-scale clinical data in human AD populations.

Applying the FFC 17-step framework to berberine reveals both strengths and shortcomings. While berberine excels as a functional food candidate, use of the FFC's 17-step framework to systematically evaluate its path from bioactive compound to functional food product demonstrates that it is not yet ready for mainstream therapeutic use without further high-quality human evidence. The next steps in berberine's development will require large, well-powered clinical trials and novel methods of delivery to determine whether it can fulfill a role as a practical means to support cognitive and metabolic health.

Abbreviations: Alzheimer's Disease (AD); AMP-activated protein kinase (AMPK); type 2 diabetes mellitus (T2DM)

REFERENCES

1. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2024 Apr 30;20(5):3708–821. DOI: https://doi.org/10.1002/alz.13809
2. Olivares D, Deshpande VK, Shi Y, Lahiri DK, Greig NH, Rogers JT, et al. N-Methyl D-Aspartate (NMDA) Receptor Antagonists and Memantine Treatment for Alzheimer's Disease, Vascular Dementia and Parkinson's Disease. *Curr Alzheimer Res.* 2012 July;9(6):746–58. DOI: https://doi.org/10.2174/156720512801322564
3. CDC. Diabetes. 2024. Type 2 Diabetes. Available from: https://www.cdc.gov/diabetes/about/about-type-2-diabetes.html
4. Ramkumar S, Raghunath A, Raghunath S. Statin Therapy: Review of Safety and Potential Side Effects. *Acta Cardiol Sin.* 2016 Nov;32(6):631–9. DOI: https://doi.org/10.6515/acs20160611a
5. Wu J, Song Y, Li H, Chen J. Rhabdomyolysis associated with fibrate therapy: review of 76 published cases and a new case report. *Eur J Clin Pharmacol.* 2009 Dec;65(12):1169–74. DOI: https://doi.org/10.1007/s00228-009-0723-7
6. Chatterjee S, Mudher A. Alzheimer's Disease and Type 2 Diabetes: A Critical Assessment of the Shared Pathological Traits. *Front Neurosci.* 2018 June 8; 12:383. DOI: https://doi.org/10.3389/fnins.2018.00383
7. Dietary Supplements and Nutraceuticals - Online ISSN: 2771-5604. Available from: https://www.ffhdj.com/index.php/DietarySupplementsNutraceuticals
8. Feng X, Sureda A, Jafari S, Memariani Z, Tewari D, Annunziata G, et al. Berberine in Cardiovascular and Metabolic Diseases: From Mechanisms to Therapeutics. *Theranostics*. 2019 Mar 16;9(7):1923–51. DOI: https://doi.org/10.7150/thno.30787

9. Zhang N, Gao Y, Yu S, Sun X, Shen K. Berberine attenuates Aβ42-induced neuronal damage through regulating circHDAC9/miR-142-5p axis in human neuronal cells. *Life Sci.* 2020 July 1; 252:117637. DOI: https://doi.org/10.1016/j.lfs.2020.117637
10. Martirosyan D, Santrosyan G, McCarthy J, Nguyen A. Metformin: Optimal dosage, interactions, and efficacy. Exploring natural alternatives for diabetes management. *Bioact Compd Health Dis*. 2025 May 21;8(5):177–203. DOI: https://doi.org/10.31989/bchd.v8i5.1624
11. Khoshandam A, Imenshahidi M, Hosseinzadeh H. Pharmacokinetic of berberine, the main constituent of Berberis vulgaris L.: A comprehensive review. *Phytother Res.* 2022;36(11):4063–79. DOI: https://doi.org/10.1002/ptr.7589
12. Ai X, Yu P, Peng L, Luo L, Liu J, Li S, et al. Berberine: A Review of its Pharmacokinetics Properties and Therapeutic Potentials in Diverse Vascular Diseases. *Front Pharmacol.* 2021 Nov 3; 12:762654. DOI: https://doi.org/10.3389/fphar.2021.762654
13. Rad SZK, Rameshrad M, Hosseinzadeh H. Toxicology effects of Berberis vulgaris (barberry) and its active constituent, berberine: a review. *Iran J Basic Med Sci.* 2017 May;20(5):516–29. DOI: https://doi.org/10.22038/ijbms.2017.8676
14. Feng X, Wang K, Cao S, Ding L, Qiu F. Pharmacokinetics and Excretion of Berberine and Its Nine Metabolites in Rats. *Front Pharmacol.* 2021 Jan 15; 11:594852. DOI: https://doi.org/10.3389/fphar.2020.594852
15. Han Y, Xiang Y, Shi Y, Tang X, Pan L, Gao J, et al. Pharmacokinetics and Pharmacological Activities of Berberine in Diabetes Mellitus Treatment. *Evid-Based Complement Altern Med ECAM.* 2021 Aug 21; 2021:9987097. DOI: https://doi.org/10.1155/2021/9987097
16. Solnier J, Zhang Y, Kuo YC, Du M, Roh K, Gahler R, et al. Characterization and Pharmacokinetic Assessment of a New Berberine Formulation with Enhanced Absorption In Vitro and in Human Volunteers. *Pharmaceutics*. 2023 Nov 1;15(11):2567. DOI: https://doi.org/10.3390/pharmaceutics15112567
17. Hua W, Ding L, Chen Y, Gong B, He J, Xu G. Determination of berberine in human plasma by liquid chromatography–electrospray ionization–mass spectrometry. *J Pharm Biomed Anal.* 2007 Aug 15;44(4):931–7. DOI: https://doi.org/10.1016/j.jpba.2007.03.022
18. Tan XS, Ma JY, Feng R, Ma C, Chen WJ, Sun YP, et al. Tissue Distribution of Berberine and Its Metabolites after Oral Administration in Rats. *PLoS ONE*. 2013 Oct 31;8(10):e77969. DOI: https://doi.org/10.1371/journal.pone.0077969
19. Chen N, Guo C e, Chen H, Chen J, Bi X, Li H, et al. Simultaneous determination of six coptis alkaloids in urine and feces by LC–MS/MS and its application to excretion kinetics and the compatibility mechanism of Jiao-Tai-Wan in insomniac rats. *Biomed Chromatogr.* 2018;32(8):e4248. DOI: https://doi.org/10.1002/bmc.4248
20. Lyu Y, Li D, Yuan X, Li Z, Zhang J, Ming X, et al. Effects of combination treatment with metformin and berberine on hypoglycemic activity and gut microbiota modulation in db/db mice. *Phytomedicine Int J Phytother Phytopharm.* 2022 July; 101:154099. DOI: https://doi.org/10.1016/j.phymed.2022.154099
21. Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI, Crişan G, et al. Berberine: Botanical Occurrence, Traditional Uses, Extraction Methods, and Relevance in Cardiovascular, Metabolic, Hepatic, and Renal Disorders. *Front Pharmacol.* 2018 Aug 21;9:557. DOI: https://doi.org/10.3389/fphar.2018.00557
22. Zhang L, Wu X, Yang R, Chen F, Liao Y, Zhu Z, et al. Effects of Berberine on the Gastrointestinal Microbiota. *Front Cell Infect Microbiol.* 2021 Feb 19;10:588517. DOI: https://doi.org/10.3389/fcimb.2020.588517
23. Lai G, Wu H, Yang K, Hu K, Zhao W, Chen X, et al. Potential Applications of Natural Components of Traditional Chinese Medicine Delivery via Nanoparticle Drug Delivery Systems in the Treatment of Alzheimer's Disease. *Int J Nanomedicine.* 2025 June 17; 20:7781–810. DOI: https://doi.org/10.2147/ijn.s525960
24. Dan L, Hao Y, Li J, Wang T, Zhao W, Wang H, et al. Neuroprotective effects and possible mechanisms of berberine in animal models of Alzheimer's disease: a systematic review and meta-analysis. *Front Pharmacol*. 2024 Jan 8;14. DOI: https://doi.org/10.3389/fphar.2023.1287750
25. Ji L, Ma J, Ma Y, Cheng Z, Gan S, Yuan G, et al. Berberine Ursodeoxycholate for the Treatment of Type 2 Diabetes: A Randomized Clinical Trial. *JAMA Netw Open.* 2025 Mar 3;8(3): e2462185. DOI: https://doi.org/10.1001/jamanetworkopen.2024.62185
26. Harrison SA, Gunn N, Neff GW, Kohli A, Liu L, Flyer A, et al. A phase 2, proof of concept, randomised controlled trial of berberine ursodeoxycholate in patients with presumed non-alcoholic steatohepatitis and type 2 diabetes. *Nat Commun.* 2021 Sept 17; 12:5503. DOI: https://doi.org/10.1038/s41467-021-25701-5
27. Ye Y, Liu X, Wu N, Han Y, Wang J, Yu Y, et al. Efficacy and Safety of Berberine Alone for Several Metabolic Disorders: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Front Pharmacol.* 2021 Apr 26; 12:653887.

DOI: https://doi.org/10.3389/fphar.2021.653887

28. Habtemariam S. Berberine pharmacology and the gut microbiota: A hidden therapeutic link. *Pharmacol Res.* 2020 May 1; 155:104722. DOI: https://doi.org/10.1016/j.phrs.2020.104722
29. Martirosyan D. Functional Food Science and Bioactive Compounds. *Bioact Compd Health*. 2025 June 30;8(6):218–29. DOI: https://doi.org/10.31989/bchd.v8i6.1667
30. Martirosyan D, Lampert T, Ekblad M. Classification and regulation of functional food proposed by the Functional Food Center. *Funct Food Sci.* 2022 Feb 7;2(2):25–46. DOI: https://doi.org/10.31989/ffs.v2i2.890
31. Baba A, Ogawa S, Yokosho K, Suzuki N, Takara T. Effects of the consumption of Acacia bark-derived proanthocyanidins on visceral fat: A randomized, double-blind, placebo-controlled, parallel-group comparative study. *Funct Foods Health Dis.* 2024 Dec 12;14(12):947–67. DOI: https://doi.org/10.31989/ffhd.v14i12.1420
32. Martirosyan D, Singh J. A new definition of functional food by FFC: what makes a new definition unique? *Funct Foods Health Dis*. 2015 July 1;5(6):209–23. DOI: https://doi.org/10.31989/ffhd.v5i6.183
33. Martirosyan D, Kanya H, Nadalet C. Can functional foods reduce the risk of disease? Advancement of functional food definition and steps to create functional food products. *Funct Foods Health Dis*. 2021 May 10;11(5):213–21. DOI: https://doi.org/10.31989/ffhd.v11i5.788
34. Sugimoto K, Fujisawa H, Nakagawa K, Yamamoto K, Suzuki N, Yamashita, et al. Anti-obesity effect of eucalyptus leaf extract containing oenothein B in healthy Japanese adults: a randomized, placebo-controlled, double-blind, parallel-group study. *Funct Foods Health Dis*. 2022 May 28;12(5):242–63. DOI: https://doi.org/10.31989/ffhd.v12i5.927
35. Martirosyan D. The emerging potential of functional foods in viral disease prevention. *Bioact Compd Health Dis*. 2020 June 30;3(6):95–9. DOI: https://doi.org/10.31989/bchd.v3i6.726
36. Lee H, Kuwabara Y, Hirose A, Makino Y, Hashimoto K, Sakata M, et al. Long-term safety study of the highly absorbable curcumin formulation TS-P1 in healthy Japanese adults: a randomized, placebo-controlled, double-blind, parallel-group comparative study. *Funct Foods Health Dis.* 2024 July 26;14(7):546–63. DOI: https://doi.org/10.31989/ffhd.v14i7.1396
37. Xie B, Chen P, Hong Y, Xu C, Zhang W. Effects of a dietary compound tablet on glucose metabolism in a hyperglycemic mouse model. *Diet Suppl Nutraceuticals.* 2025 June 6;4(06):1–11.
38. Martirosyan D, Stratton S. Quantum and tempus theories of function food science in practice. *Funct Food Sci*. 2023 May 31;3(5):55–62. DOI: https://doi.org/10.31989/ffs.v3i5.1122
39. Imenshahidi M, Hosseinzadeh H. Berberine and barberry (Berberis vulgaris): A clinical review. *Phytother Res.* 2019;33(3):504–23. DOI: https://doi.org/10.1002/ptr.6252
40. Li Z, Geng YN, Jiang JD, Kong WJ. Antioxidant and Anti-Inflammatory Activities of Berberine in the Treatment of Diabetes Mellitus. *Evid-Based Complement Altern Med ECAM.* 2014; 2014:289264. DOI: https://doi.org/10.1155/2014/289264
41. Jin Y, Liu S, Ma Q, Xiao D, Chen L. Berberine enhances the AMPK activation and autophagy and mitigates high glucose-induced apoptosis of mouse podocytes. *Eur J Pharmacol.* 2017 Jan 5;794:106–14. DOI: https://doi.org/10.1016/j.ejphar.2016.11.037
42. Araj-Khodaei M, Ayati MH, Azizi Zeinalhajlou A, Novinbahador T, Yousefi M, Shiri M, et al. Berberine-induced glucagon-like peptide-1 and its mechanism for controlling type 2 diabetes mellitus: a comprehensive pathway review. *Arch Physiol Biochem.* 2024 Nov 1;130(6):678–85. DOI: https://doi.org/10.1080/13813455.2023.2258559
43. Sarna LK, Wu N, Hwang SY, Siow YL, O K. Berberine inhibits NADPH oxidase mediated superoxide anion production in macrophages. *Can J Physiol Pharmacol.* 2010 Mar;88(3):369–78. DOI: https://doi.org/10.1139/y09-136
44. Laein GD, Boumeri E, Ghanbari S, Bagherian A, Ahmadinasab F, Poudineh V, et al. Neuroprotective effects of berberine in preclinical models of ischemic stroke: a systematic review. *BMC Pharmacol Toxicol.* 2025 Feb 21;26(1):40. DOI: https://doi.org/10.1186/s40360-025-00843-0
45. Zhao C, Su P, Lv C, Guo L, Cao G, Qin C, et al. Berberine Alleviates Amyloid β-Induced Mitochondrial Dysfunction and Synaptic Loss. *Oxid Med Cell Longev.* 2019 May 2; 2019:7593608. DOI: https://doi.org/10.1155/2019/7593608
46. Cai Z, Wang C, He W, Chen Y. Berberine Alleviates Amyloid-Beta Pathology in the Brain of APP/PS1 Transgenic Mice via Inhibiting β/γ-Secretases Activity and Enhancing α-Secretases. *Curr Alzheimer Res.* 2018;15(11):1045–52. DOI: https://doi.org/10.2174/1567205015666180702105740
47. Chen Y, Li K, Zhao H, Hao Z, Yang Y, Gao M, et al. Integrated lipidomics and network pharmacology analysis to reveal the mechanisms of berberine in the treatment of hyperlipidemia. *J Transl Med.* 2022 Sept 8;20:412.

DOI: https://doi.org/10.1186/s12967-022-03623-0

48. Mirhadi E, Rezaee M, Malaekeh-Nikouei B. Nano strategies for berberine delivery, a natural alkaloid of *Berberis*. *Biomed Pharmacother.* 2018 Aug 1; 104:465–73.
DOI: https://doi.org/10.1016/j.biopha.2018.05.067
49. Zhang X, Zhou JS, Wu HJ, Guo Y. Adhesive hydrogels containing berberine and mesoporous silica nanocarriers: a potential therapy for neurovascular dysfunction and cognitive decline in Alzheimer's disease. *J Biomater Sci Polym Ed*. 2025 June 28;1–19.
DOI: https://doi.org/10.1080/09205063.2025.2519867
50. Harrison SA, Gunn N, Neff GW, Kohli A, Liu L, Flyer A, et al. A phase 2, proof of concept, randomised controlled trial of berberine ursodeoxycholate in patients with presumed non-alcoholic steatohepatitis and type 2 diabetes. *Nat Commun.* 2021 Sept 17;12(1):5503.
DOI: https://doi.org/10.1038/s41467-021-25701-5
51. Zhang Y, Gu Y, Ren H, Wang S, Zhong H, Zhao X, et al. Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study). *Nat Commun.* 2020 Oct 6;11(1):5015.
DOI: https://doi.org/10.1038/s41467-020-18414-8
52. Pu Z, Wen H, Jiang H, Hou Q, Yan H. Berberine improves negative symptoms and cognitive function in patients with chronic schizophrenia via anti-inflammatory effect: a randomized clinical trial. Chin Med. 2023 Apr 17; 18:41.
DOI: https://doi.org/10.1186/s13020-023-00746-4
53. Zhang Q, Bian H, Guo L, Zhu H. Berberine Preconditioning Protects Neurons Against Ischemia via Sphingosine-1-Phosphate and Hypoxia-Inducible Factor-1α. *Am J Chin Med.* 2016 Aug 1;44(5):927–941
DOI: https://doi.org/10.1142/s0192415x16500518
54. Zhang X, Zhang X, Wang C, Li Y, Dong L, Cui L, et al. Neuroprotection of early and short-time applying berberine in the acute phase of cerebral ischemia: Up-regulated pAkt, pGSK and pCREB, down-regulated NF-κB expression, ameliorated BBB permeability. *Brain Res.* 2012 June 12;1459:61–70.
DOI: https://doi.org/10.1016/j.brainres.2012.03.065
55. Liu YL, Guo T, Zhang YJ, Tang SC, Zhao XM, He HY, et al. Berberine Alleviates Ischemic Brain Injury by Enhancing Autophagic Flux via Facilitation of TFEB Nuclear Translocation. *Am J Chin Med.* 2024 Jan;52(01):231–52.
DOI: https://doi.org/10.1142/s0192415x24500101
56. Maleki SN, Aboutaleb N, Souri F. Berberine confers neuroprotection in coping with focal cerebral ischemia by targeting inflammatory cytokines. *J Chem Neuroanat.* 2018 Jan 1; 87:54–9.
DOI: https://doi.org/10.1016/j.jchemneu.2017.04.008