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Review Article

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Berberine: Structure, Applications, Efficacy, and Recent Achievements

Habibollah Sedaghat [1,3]. Morteza Chaboki* [1,3] and Mahdi Esmaeilzaeh [2,3]

[1] IR_TAK_41/796234, Development, Economy and Entrepreneurship Holding (TAK) Tehran, Iran
[2] Head of Department of cell and molecular biology, Center for neuroscience research, Georgia
[3] Scientific Research Publishing House (SRPH) Shirvan, Iran

***Corresponding Author:**
m.chaboki.kn@gmail.com

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ABSTRACT

Berberine, a natural isoquinoline alkaloid, has attracted considerable attention for its diverse pharmacological properties. Extracted from plants like "Berberis" species and "Coptis chinensis", berberine has been used in traditional medicine systems for centuries. Modern research has unveiled its significant potential in managing metabolic syndromes, cardiovascular disorders, microbial infections, and cancer. This review provides an in-depth analysis of berberine's mechanisms of action, therapeutic applications, clinical efficacy, and safety profile. Although promising, challenges such as low bioavailability and limited high-quality clinical trials need to be addressed to realize its full potential.

Keywords: Berberine, Metabolic syndromes, Cardiovascular disorders, Microbial infections, Cancer, Therapeutic applications, Clinical efficacy

Introduction

Berberine is a naturally occurring isoquinoline alkaloid extracted from various medicinal plants, including "Berberis" species, "Coptis chinensis", and "Phellodendron amurense". It is characterized by a quaternary ammonium salt structure, giving it a distinct yellow color and bitter taste. The molecular formula of berberine is \(C_{20}H_{18}NO_4\), and its structure comprises a benzodioxolo ring fused to an isoquinoline framework (fig1). This unique structure contributes to its diverse biological activities, ranging from antimicrobial effects to metabolic regulation. Berberine's role as a bioactive compound has made it a focal point in pharmacological research [1-3].

Extensive research over the last few decades has demonstrated berberine's potential across a wide range of therapeutic applications. Studies have highlighted its efficacy in treating metabolic disorders like type 2 diabetes, dyslipidemia, and obesity. Additionally, berberine exhibits antimicrobial, anti-inflammatory, and antioxidant properties, as well as anticancer effects. Both preclinical and clinical studies have provided evidence of its ability to regulate glucose metabolism, lipid profiles, and gut microbiota composition [1 ,3]. However, despite its promising results, limitations such as poor bioavailability and a lack of large-scale clinical trials have impeded its widespread adoption in clinical practice[3,4].

The importance of berberine lies in its multifaceted mechanisms of action, which target various pathways involved in chronic and infectious diseases. Its ability to activate AMP-activated protein kinase (AMPK), regulate lipid metabolism, and suppress inflammation positions it as a potential therapeutic agent for managing complex conditions like metabolic syndrome and cardiovascular diseases. Furthermore, berberine's natural origin and traditional use make it a compelling alternative or complementary treatment option in integrative medicine. Understanding its pharmacological properties and clinical applications is essential for optimizing its therapeutic use [5,6].

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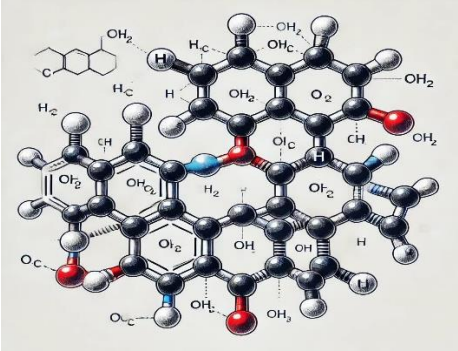

Fig 1. schematic figure of the berberine molecule

The aim of this study is to provide a comprehensive review of berberine's pharmacological mechanisms, therapeutic potential, and clinical applications. By analyzing existing research, this study seeks to address the gaps in current knowledge, particularly regarding its efficacy, safety, and limitations. The findings aim to guide future research and clinical applications, with a focus on overcoming challenges such as bioavailability and standardizing its use across diverse populations [1,7].

Materials and Methods

A systematic literature search was conducted using PubMed, Scopus, and Google Scholar databases. Keywords included "berberine," "pharmacology," "clinical trials," and "chronic disease management." Studies published between January 2000 and October 2024 were included. Articles were screened for relevance, focusing on preclinical studies, randomized controlled trials (RCTs), and meta-analyses. Exclusion criteria included studies with limited methodology or non-English language publications.

Result

1-Pharmacological Mechanisms of Berberine

1.1 Activation of AMPK Pathway

AMP-activated protein kinase (AMPK) is a master regulator of energy homeostasis. Berberine activates AMPK in various tissues, improving glucose uptake, lipid metabolism, and mitochondrial function (fig 2). This mechanism underpins many of its antidiabetic and cardioprotective effects [1,2]

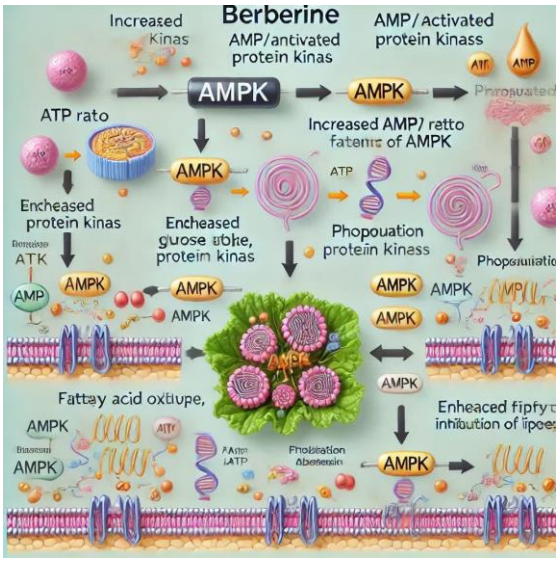

Fig 2. schematic figure of the berberine effect on AMPK pathway

1.2 Regulation of Lipid Metabolism

Berberine upregulates LDL receptor (LDLR) expression in hepatocytes, enhancing LDL cholesterol clearance from the bloodstream (fig 3). It also suppresses lipogenesis by inhibiting sterol regulatory element-binding protein 1 (SREBP1) [3,6]

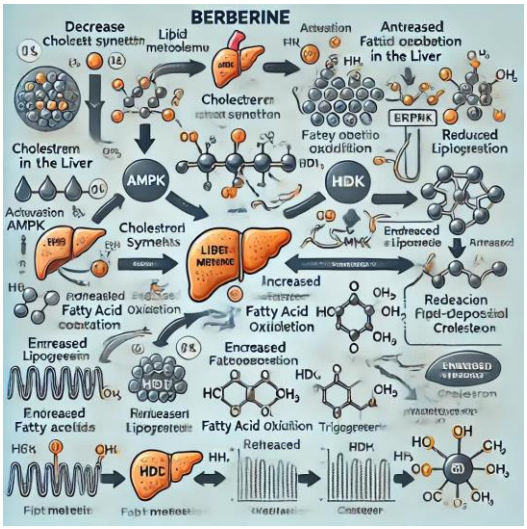

Fig 3. schematic figure of the berberine effect on lipid metabolism

1.3 Anti-Inflammatory Effects

Berberine inhibits nuclear factor-kappa B (NF-ϰB), a key transcription factor involved in the production of inflammatory cytokines such as TNF-α, IL-6, and IL-1β (fig 4). This property is crucial for its role in managing chronic inflammatory conditions [5].

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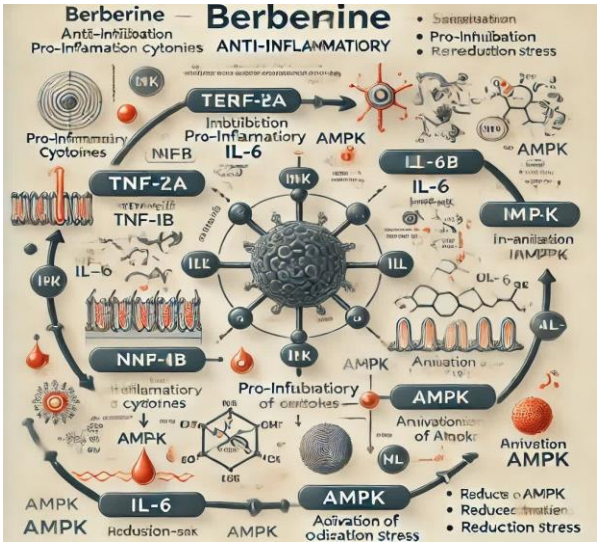

Fig 4. schematic figure of Anti-Inflammatory effects of berberine

1.4 Antioxidant Properties

Berberine reduces oxidative stress by enhancing antioxidant enzyme activities, such as superoxide dismutase (SOD) and catalase, while suppressing reactive oxygen species (ROS) production (fig 5) [7]

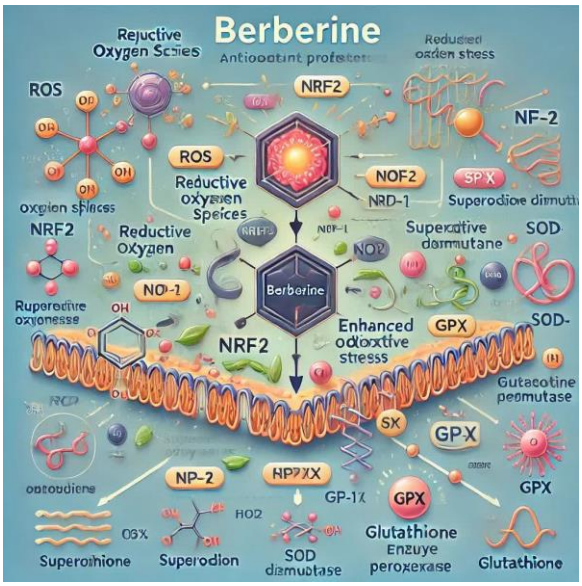

Fig 5. schematic figure of Anti-oxidant properties of berberine

1.5 Microbial Inhibition

Berberine disrupts microbial DNA and protein synthesis, exhibiting antimicrobial activity against bacteria, fungi, and viruses (fig 6) [2,4]

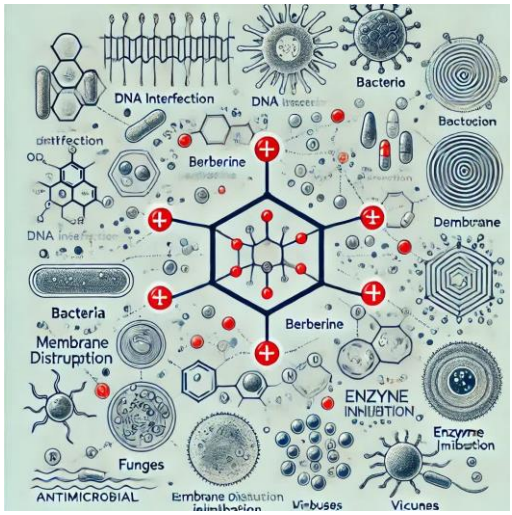

Fig 6. schematic figure of Anti-microbial effects of berberine

2. Therapeutic Applications

2.1 Metabolic Disorders

Type 2 Diabetes Mellitus (T2DM):

Multiple RCTs have shown berberine's efficacy in reducing fasting plasma glucose, HbA1c, and postprandial glucose levels, often comparable to first-line drugs like metformin (fig 7 and 8). It improves insulin sensitivity by activating AMPK and modulating gut microbiota [3,4].

Obesity:

Berberine inhibits adipocyte differentiation and promotes lipid breakdown via AMPK activation. Studies indicate modest but significant reductions in body weight and waist circumference [1].

Dyslipidemia:

Berberine effectively reduces LDL cholesterol, total cholesterol, and triglycerides, while increasing HDL cholesterol(fig 9 and 10). It achieves this by modulating liver lipid metabolism pathways [5].

2.2 Cardiovascular Health

Heart Failure and Hypertension:

Preclinical studies suggest that berberine improves cardiac function by enhancing mitochondrial efficiency and reducing fibrosis. It also exerts vasodilatory effects through endothelial nitric oxide production [6].

Atherosclerosis:

Berberine reduces plaque formation by inhibiting foam cell formation and reducing vascular inflammation [7].

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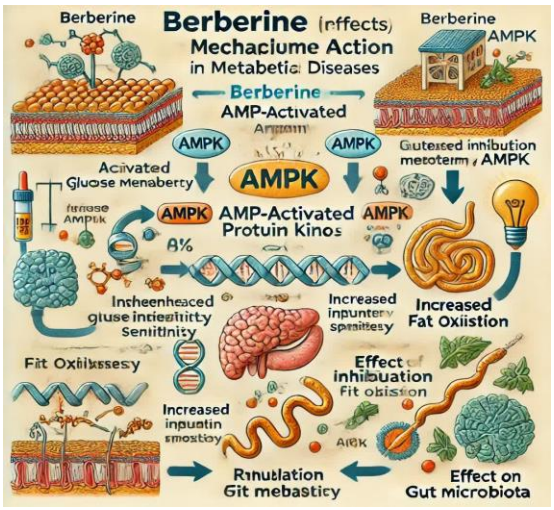

Fig 7. schematic figure of berberine effects on metabolic disorders

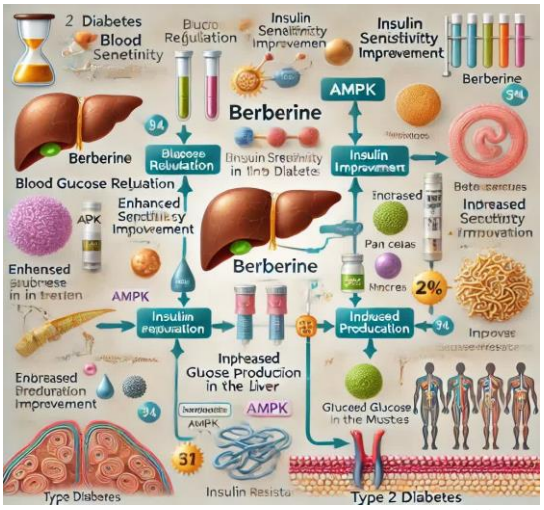

Fig 8. schematic figure of berberine effects on Type 2 Diabetes Mellitus (T2DM)

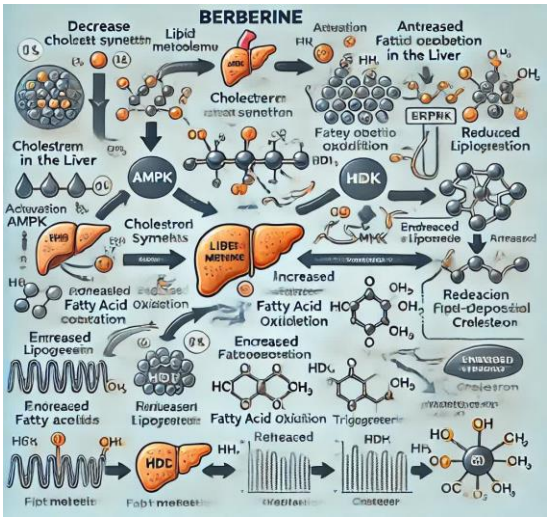

Fig 9. schematic figure of berberine effects on lipids metabolism

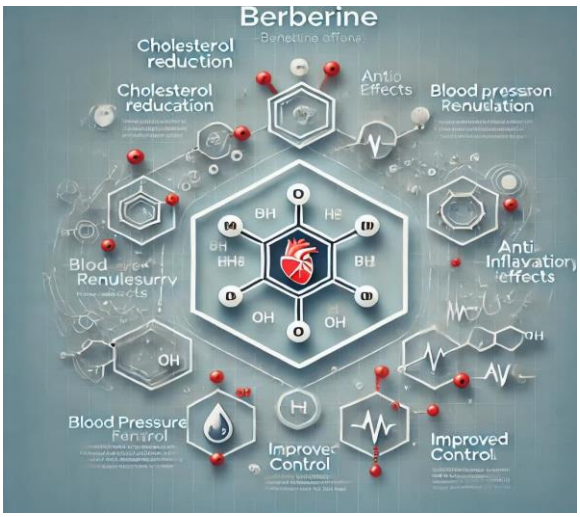

Fig 10. schematic figure of berberine effects on cholesterol level

2.3 Infectious Diseases

Antibacterial Activity:

Effective against Gram-positive and Gram-negative bacteria, including "Escherichia coli", "Staphylococcus aureus", and "Helicobacter pylori" [3].

Antiviral Properties:

Berberine inhibits viral replication in diseases like hepatitis B, herpes simplex, and influenza [1].

Antifungal Activity:

Berberine shows activity against fungi like "Candida albicans" by disrupting fungal cell walls and biofilms [4].

2.4 Cancer Therapy

Berberine induces apoptosis, inhibits proliferation, and suppresses angiogenesis in various cancers, including colorectal, breast, and liver cancers (fig 11). It exerts its anticancer effects through multiple pathways, such as p53 activation and inhibition of the PI3K/AKT/mTOR pathway [1,2].

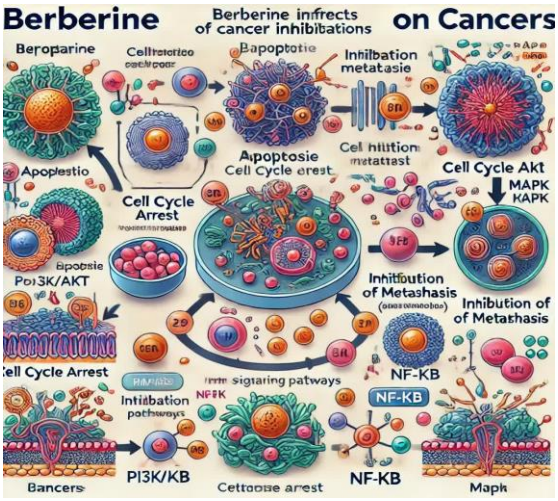

Fig 11. schematic figure of berberine effects on cancers

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2.5 Gut Microbiota Modulation

Berberine alters the gut microbiota composition, increasing beneficial bacteria like *Akkermansia muciniphila* and reducing harmful species, thereby contributing to its metabolic and anti-inflammatory effects [3].

2.6 Berberine effect on alzheimer's disease (AD)

Fig 12 shows the schematic representation of berberine's effects on Alzheimer's disease. It illustrates its neuroprotective mechanisms, including interactions with amyloid-beta plaques and tau proteins, while reducing oxidative stress and inflammation.

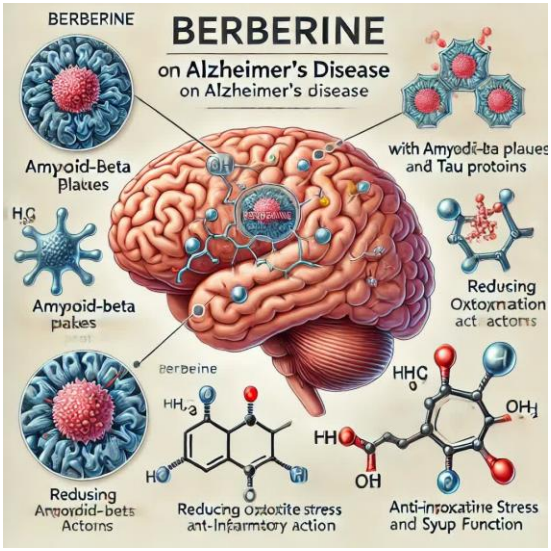

Fig 12. schematic figure of berberine effects on Alzheimer's Disease (AD)

Berberine, exhibits promising neuroprotective properties for treating Alzheimer's disease (AD) through several mechanisms:

2.6.1. Reduction of Amyloid-β Accumulation:

Berberine decreases the production of amyloid-beta (Aβ), a key component of the plaques associated with Alzheimer's. It achieves this by inhibiting β-secretase (BACE1), an enzyme involved in Aβ generation, and by reducing the phosphorylation of tau proteins, which contributes to neurofibrillary tangles [8, 9].

2.6.2. Anti-inflammatory and Antioxidant Effects:

By mitigating oxidative stress and suppressing pro-inflammatory cytokines such as TNF-α and IL-1β, berberine helps to alleviate the neuronal damage caused by chronic inflammation and reactive oxygen species, both of which are prominent in AD [8, 9].

2.6.3. Modulation of Autophagy:

Berberine enhances autophagy, a cellular process that removes damaged proteins and organelles, thereby improving neuronal health and function [8, 9].

2.6.4. Anti-apoptotic Effects:

It protects neurons from apoptosis (programmed cell death) by regulating mitochondrial function and reducing oxidative damage. Berberine also influences the expression of key apoptotic regulators, favoring cell survival in neural tissues [9].

2.6.5. Cholinergic Protection:

Berberine has been shown to inhibit acetylcholinesterase (AChE), an enzyme that degrades acetylcholine, a neurotransmitter critical for memory and learning. This helps preserve cognitive function in AD models [8].

3. Clinical Efficacy and Limitations

3.1 Clinical Trials and Meta-Analyses

A meta-analysis of 14 RCTs (n = 1,068) found that berberine significantly reduced fasting blood glucose and LDL cholesterol levels compared to placebo [7]. Another review highlighted its efficacy in improving metabolic parameters in patients with polycystic ovary syndrome (PCOS) [3].

3.2 Bioavailability Issues

Berberine's low oral bioavailability (<1%) remains a significant challenge due to poor absorption and rapid metabolism in the gut and liver. Strategies to enhance its bioavailability include nanoparticle formulations, liposomes, and co-administration with absorption enhancers like piperine [1].

3.3 Side Effects

Common: Gastrointestinal discomfort, such as diarrhea, nausea, and abdominal cramps.

Serious: Potential interactions with drugs metabolized by CYP450 enzymes, increasing the risk of adverse effects [4].

Various pharmaceutical forms of berberine

Berberine is available in various pharmaceutical forms to suit different therapeutic needs and preferences. Common forms include:

1. Oral Forms:

Tablets: Solid dosage form for easy swallowing; often coated for controlled release or to improve taste.

Capsules: Encased in gelatin or plant-based shells, containing powdered or pure berberine extract.

Softgels: Encapsulated liquid berberine for enhanced absorption.

Powder: Typically sold in bulk for mixing with liquids or food; allows for flexible dosing.

2. Liquid Forms:

Tinctures: Berberine extract dissolved in alcohol or glycerin for direct ingestion or dilution.

Syrups: Sweetened liquid form for easier consumption, especially for children.

3. Topical Forms - Creams and Ointments:

Used for skin conditions or localized infections, leveraging berberine's antimicrobial and anti-inflammatory properties.

Gels: Water-based formulations for easy application and absorption on the skin or mucous membranes.

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4. Injectable Form - Intravenous (IV) or Intramuscular (IM) Preparations:
Less common but may be used in research or specialized treatments under medical supervision.
5. Other Forms - Suppositories:
Occasionally formulated for rectal or vaginal use to target localized infections or inflammation.
Herbal Teas: Contains berberine-rich plant extracts, typically from "Berberis" or "Coptis" species, for systemic or digestive health.
6. Combination Products - Blended Supplements: Berberine is often combined with other compounds (e.g., milk thistle, alpha-lipoic acid, or cinnamon) to enhance its efficacy, particularly for metabolic and cardiovascular health. Each form has specific advantages depending on the condition being treated, bioavailability requirements, and patient preference.

Berberine Drink vs. Other Forms of Berberine
Berberine drinks are a growing trend as a convenient and enjoyable way to consume berberine, offering unique benefits compared to other pharmaceutical forms such as capsules, tablets, powders, and topical applications (table 1).

Table1. Comparison of Berberine Drink and Other Forms of Berberine

Form	Benefits	Drawbacks	Best Suited For
Berberine Drink	-Easy to consume, especially for those who dislike pills. - Provides hydration. - Faster absorption than solid forms. - Can include added nutrients.	- Natural bitterness may require flavoring. - Lower berberine concentration. - Less stable without preservatives.	Individuals seeking a palatable option with hydration.
Capsules	- Precise dosing. - Convenient and portable. - Longer shelf life.	- Absorption is slower compared to liquids. - May be difficult to swallow for some individuals.	Consistent daily dosing with convenience.
Tablets	- Affordable. - Can offer extended-release formulations for sustained effects.	- Can leave a bitter aftertaste. - May cause discomfort for sensitive stomachs.	Cost-effective and long-term use.
Powders	- Customizable dosing. - Can be mixed into beverages or food. - Suitable for high dosages.	- Requires preparation (mixing). - Bitter taste may need masking.	Flexible dosing and combining with other nutrients.
Topical Forms	- Localized application (e.g., for skin infections or inflammation). - No systemic absorption, minimizing side effects.	- Limited to external use. - Ineffective for internal conditions such as diabetes or metabolic disorders.	Treating skin issues, wounds, or localized inflammation.

Why Choose a Berberine Drink? - Ideal for individuals who dislike swallowing pills or prefer a flavorful experience. - Provides hydration alongside the benefits of berberine. - May be enriched with complementary ingredients like probiotics or herbal extracts for enhanced effects. While drinks offer a convenient and enjoyable way to consume berberine, capsules and tablets remain the go-to options for precise dosing and long-term stability. Each form has its place, depending on individual preferences and therapeutic goals.

Steps for Producing a Berberine Drink:
Creating a berberine-based drink involves several steps to ensure consistency, safety, and efficacy. Below is a general outline for producing a berberine drink (fig 13):
1. Sourcing and Extraction of Berberine - Raw Material Selection:
Source berberine-rich plants such as "Berberis" species, "Coptis chinensis", or "Hydrastis canadensis". **Extraction Process**: Use techniques like water or ethanol extraction to obtain berberine alkaloids from the plant material.
Grinding: Dry and grind the plant material to increase surface area for extraction.

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Solvent Use: Immerse the material in a suitable solvent (e.g., water, ethanol) to dissolve berberine.
Filtration: Filter the solution to remove plant debris. - **Concentration**: Evaporate the solvent under reduced pressure to concentrate the berberine extract.
2. Formulation Development - Dilution:
Dilute the berberine extract to the desired concentration for drink preparation.
Additives: - Sweeteners (e.g., stevia, honey) to improve taste. - Flavoring agents (e.g., citrus, mint, or herbal flavors). - Preservatives (e.g., potassium sorbate, citric acid) to extend shelf life. - Functional additives (e.g., vitamins, electrolytes, or probiotics) to enhance health benefits.
pH Adjustment: Adjust the pH to ensure stability and taste compatibility.
3. Mixing and Homogenization:
Use high-speed mixers to blend the berberine solution and additives uniformly. - Perform homogenization to ensure a smooth texture and even distribution of ingredients.

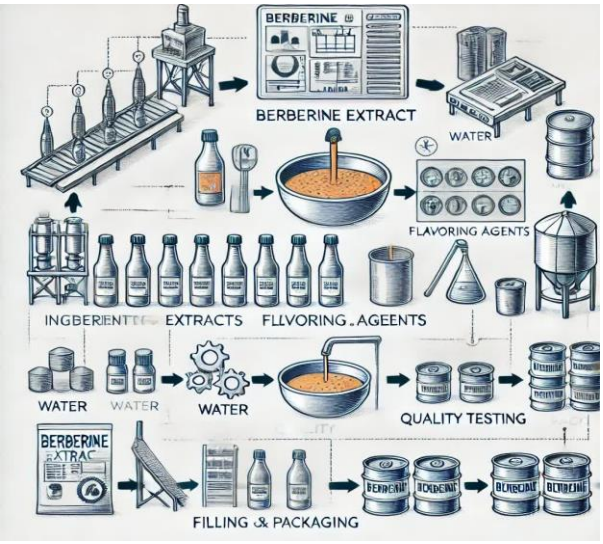

Fig 13. schematic figure of steps for producing a berberine drink

4. Pasteurization or Sterilization:
Heat the mixture to kill any pathogens and extend shelf life while preserving bioactive compounds. **Pasteurization**: Gentle heating for short periods.
UHT (Ultra-High Temperature) Treatment: For long shelf life without refrigeration.
5. Filtration:
Pass the drink through fine filters to remove any particulate matter and ensure clarity.
6. Packaging - Bottling:
Use glass or food-grade plastic bottles for packaging. - **Sealing**: Ensure airtight sealing to prevent contamination.
Labeling: Include ingredient list, berberine concentration, health benefits, usage instructions, and expiry date.
7. Quality Control:
Test for:
Berberine concentration (using HPLC or similar techniques).
Microbial safety (check for bacteria, yeast, and mold). - Stability (shelf life and preservation of active ingredients over time).
Taste and texture consistency
8. Distribution:
Store and distribute under appropriate conditions (e.g., cool, dry environments) to maintain product quality.
This process ensures that the berberine drink is safe, palatable, and effective for consumer use

Discussion

In this review, we have summarized the diverse pharmacological actions and clinical applications of berberine, focusing on its role in treating metabolic disorders, cardiovascular diseases, infections, and cancer. Our findings support the growing body of evidence that berberine has significant therapeutic potential, especially in managing type 2 diabetes, dyslipidemia, and obesity. Additionally, berberine's anti-inflammatory, antimicrobial, and antioxidant properties, as well as its ability to modulate gut microbiota, further contribute to its versatility. However, despite its promising efficacy, challenges such as poor bioavailability and the need for larger clinical trials remain limitations that hinder its clinical use [3,4]. When comparing the findings of this study with previous research, we observe a consistent pattern in the therapeutic effects of berberine across various conditions, which aligns with the conclusions of prior meta-analyses and clinical trials [3,4]. Our review corroborates earlier studies that highlighted berberine's ability to activate AMP-activated protein kinase (AMPK) and regulate glucose metabolism, as well as its lipid-lowering effects. Moreover, our focus on its impact on gut microbiota composition expands on previous work, offering a more comprehensive understanding of its multifactorial benefits [1-9].

Conclusion

Berberine stands out as a versatile bioactive compound with vast therapeutic potential fig 14). While challenges such as poor bioavailability persist, advances in formulation technologies and deeper insights into its mechanisms of action are paving the way for its broader clinical application. Future research should focus on optimizing its pharmacokinetics, understanding its molecular pathways, and validating its efficacy through large-scale clinical trials.

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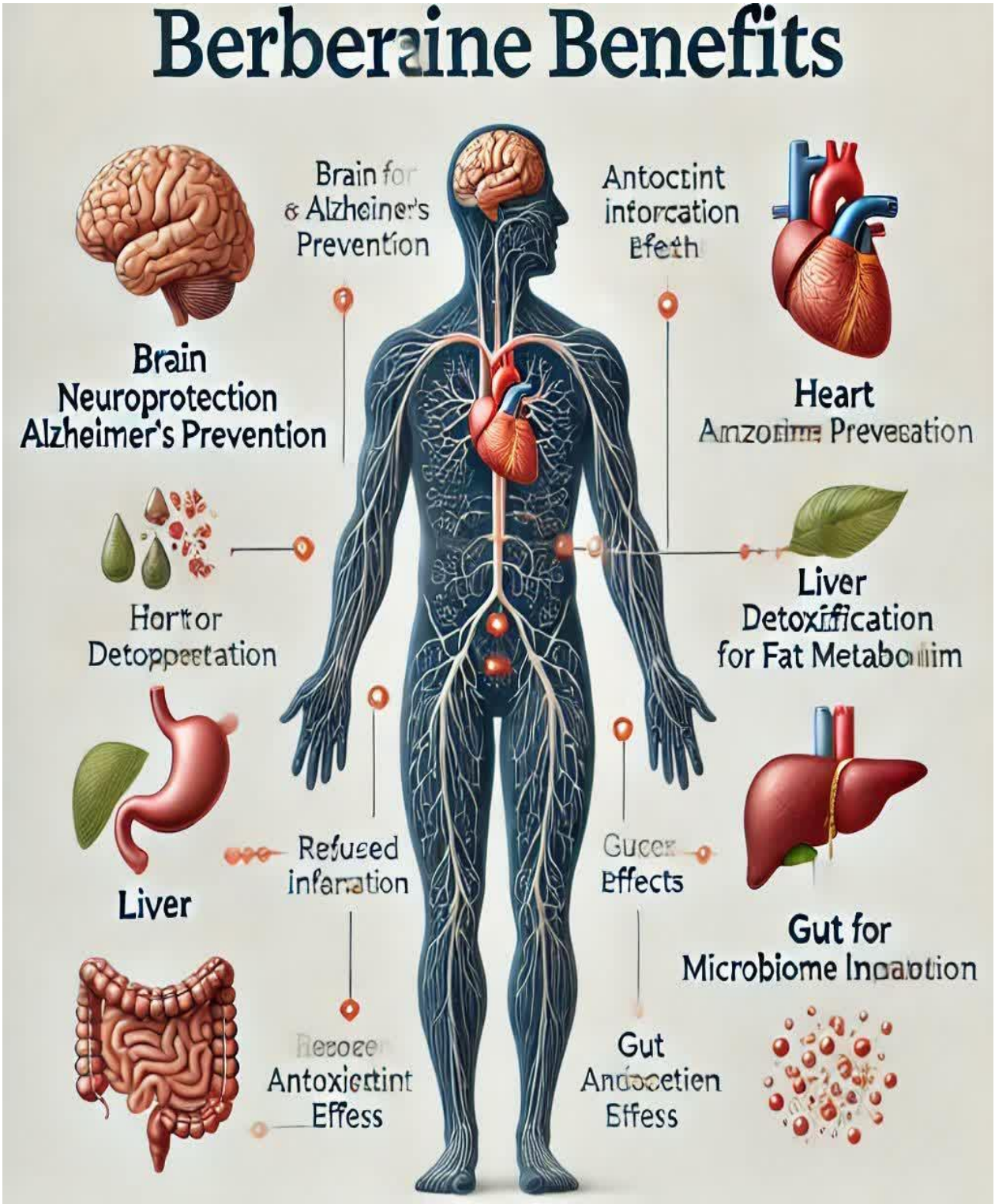

Fig 14. schematic figure of the berberine on the human body

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