Proceedings of ICMMGH 2027 Symposium: Clinical OMICS for Drug Discovery and Personalized Medicine
DOI: 10.54254/2753-8818/2027.MB38006

Multi-target Pharmacological Effects and Bioavailability Enhancement Strategies of Berberine

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Abstract. Berberine is a naturally occurring isoquinoline alkaloid with various pharmacological activities and putative therapeutic uses. Recent research has shown its anti-inflammatory and antioxidant, metabolic regulatory, anticancer, neuroprotective, and cardiovascular protective actions by modulating diverse molecular targets and signaling pathways. Many in vivo effects of berberine may also be partially mediated by gut-derived metabolites rather than parent berberine alone. The therapeutic use of berberine is restricted because of its poor oral bioavailability due to its low solubility and membrane permeability, P-glycoprotein-mediated (P-gp) intestinal efflux, high extent of intestinal and hepatic metabolism, and complex tissue distribution. Several strategies have been explored for overcoming limitations of berberine, such as structural modification, nanoparticle-based delivery systems, novel physical formulation, and absorption enhancement. These investigations have shown potential for enhancing berberine delivery, absorption, or systemic exposure, though many have been limited to preclinical data. Further research is curbed by its complexity in multi-target mechanism and its challenges of clinical translation and pharmacokinetic variability. Future research should coordinate mechanistic exploration, pharmaceutical formulation, pharmacokinetic assessment, and human clinical studies to reveal a link between improved bioavailability and therapeutic actions. Overall, resolving these limitations may be helpful to develop better efficacy and more reliable therapeutic uses of berberine.

Keywords: berberine, multi-target pharmacology, pharmacological effects, oral bioavailability, pharmacokinetics

1. Introduction

Berberine, an isoquinoline alkaloid, is a natural product and a major bioactive constituent isolated from a number of medicinal herbs, especially Coptidis Rhizoma. It has garnered significant research interest due to its diverse pharmacological properties and its potential application in the treatment of various disorders. Instead of a specific molecular target, berberine can exert its influence through modulation of multiple signaling pathways and biological processes. Berberine has been reported in the literature to exert anti-inflammatory, antioxidant, metabolic, anticancer, neuroprotective, and cardiovascular protective properties. These multifaceted pharmacological properties of berberine

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DOI: 10.54254/2753-8818/2027.MB38006

suggest that it might have immense potential in the treatment of metabolic disorders, cancers, neurological diseases, and cardiovascular diseases [1, 2].

These advantageous biological effects have been restricted for berberine in clinical pharmacological application because of its unfavorable pharmacokinetics. For the most part, berberine exhibits poor permeability in P-glycoprotein efflux and extensive metabolism in the intestine and liver, which impedes its bioavailability after oral dosage [1, 2]. Its pharmacokinetic profile and tissue distribution could additionally impact the focusing of berberine in certain target tissues. Plasma concentrations of parent berberine after oral administration are generally very low, and some of its pharmacological effects may result from local actions in the intestine and its metabolites rather than relying entirely on circulating parent berberine. Due to this, its solid pharmacological impacts noticed in exploration could not be in immediate connection with the high systemic presentation after standard oral ingestion.

Intriguing strategies have been examined to enhance berberine's delivery and improve its pharmacological execution to settle such restrictions. Chemical modification of its structure could create berberine derivatives with changed pharmacological and pharmacokinetic properties, and nanoparticle-based drug conveyance systems supply possibilities to enhance pharmaceutical stability and focused conveyance. New physical formulations, for instance, micellar, could further advance its openness without changing its basic substance structure. Absorption enhancers have additionally been examined for the improvement of tissue absorption [2].

This article concentrates on the significant pharmacological activities and the sub-molecular mechanisms of berberine; investigate the components for its poor bioavailability; and survey the ongoing methodology to enhance its ingestion and delivery. The restrictions of current examinations and potential points for further improvement and clinical utilization are discussed.

2. Pharmacological effects of berberine

2.1. Anti-inflammatory and antioxidant effects

Berberine possesses anti-inflammatory and antioxidant effects by modulating several signaling pathways. The two actions are interrelated. Excess production of reactive oxygen species (ROS) can drive inflammatory processes and, conversely, ongoing inflammation can accentuate the production of ROS, resulting in further oxidative stress. Berberine potentially offers a therapeutic benefit in its ability to attenuate both oxidative stress and inflammatory signaling processes.

One such mechanism is mediated through the sirtuin 1 (SIRT1)/nuclear factor eryroid 2-realted factor 2 (NRF2)/nuclear factor kappa B(NF-κB) signaling pathway. In an animal model of lipopolysaccharide-induced cognitive impairment in mice, berberine treatment ameliorated oxidative and inflammatory damage by modulation of the SIRT1/NRF2/NF-κB pathway [3]. NRF2 is implicated in the capacity of, NF-κB is known for regulating inflammatory reactions. The above observations indicate that berberine potentially exerts action along with anti-inflammatory signaling, which may explain its protective role in ameliorating lipopolysaccharide (LPS)-induced cognitive impairment [3].

Berberine has been reported as a multi-targeting agent having potential pharmacological significance in heart failure [4]. Berberine's actions are implicated in several molecular targets and several biological processes involved with inflammation, oxidative stress, and cardiovascular function [4]. Although berberine does not act through a single molecular process, it affects molecular mechanisms that may interconnect in various ways to influence a cellular protective action.

DOI: 10.54254/2753-8818/2027.MB38006

Collectively, the results of these studies suggest that berberine's anti-inflammatory and antioxidant activities are interrelated processes within its overall pharmacological action. Modulation of such pathways as SIRT1/NRF2/NF-κB can potentially modulate both inflammation and oxidative stress, thus providing a mechanism for certain of the observed protective actions reported in preclinical animal models [3, 4].

2.2. Metabolic effects

Glucose metabolism and lipids can positively influence glucose and lipid metabolism by modulating metabolic signaling [5]. Research indicates that berberine could positively affect insulin sensitivity and metabolic dysfunction by targeting a variety of molecular targets in energy metabolism and regulating hepatic metabolism.

By activating hepatic liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) pathways, berberine ameliorated the development of insulin in fructose-fed mice [5]. AMPK is a crucial energy metabolism regulator. Activation of the AMPK pathway can affect the utilization of glucose and fat. The above results indicate that the hepatic energy metabolism regulation is one of the mechanisms through which berberine positively affects insulin sensitivity [5].

Recent studies identified another molecular target, aldo-keto reductase family 1 member B10 (AKR1B10), in the metabolic activity of berberine. Berberine directly targets AKR1B10 and glucose metabolism disorders caused by non-alcoholic fatty liver disease (NAFLD) [6]. This study shows that the metabolic activity of berberine does not only depend on one metabolic pathway but may be in direct interaction with one or more specific metabolic proteins.

The above studies indicate that berberine regulates glucose metabolism and lipid metabolism mechanisms. Activation of the hepatic LKB1/AMPK/PGC-1α and modulation of AKR1B10 are two potential mechanisms responsible for the metabolic actions of berberine. However, these two findings are primarily on a preclinical level, and further research in clinical settings is required to know how well these mechanisms can be translated to metabolic disease in human beings [5, 6].

2.3. Anticancer effects

Evidence points to the effects of berberine that regulate a number of cellular and molecular mechanisms in multiple cancer cells. Anticancer actions have been linked to inhibition of proliferation, induction of apoptosis, inhibition of cancer cell invasion, as well as regulation of the activities of the molecular signaling pathways that are involved in cancer progression [7].

Several types of malignancies, such as breast, lung, colorectal, liver, gastric, ovarian, cervical, and prostate, have all reported berberine anticancer mechanisms are reported to include regulation of cell proliferation as well as apoptosis and processes that contribute to migration and invasion. The extensive range of cancer cells in which berberine is reported to have anticancer activities also suggests that berberine is likely not to progression via specific target. Instead, multiple pathways have been reported that are linked to cancer cell development and progression [7].

Recent reports also indicate multi-target actions of berberine in cancer. A study reported the anticancer activities of Coptidis Rhizoma and berberine for the past 10 years that suggested the potential roles in affecting tumor growth and progression [8]. Pharmacokinetics and poor bioavailability, on the other hand, are the concerns that could limit the further application of the two agents in cancer [8].

DOI: 10.54254/2753-8818/2027.MB38006

All in all, currently available evidence shows that berberine has a broad-spectrum anticancer potential via the actions on multiple important processes that are involved in tumor development. Further studies are, however, needed to reveal the potential application to translate the anti-cancer effects into treatment [7, 8].

2.4. Neuroprotective and cognitive effects

Berberine has demonstrated properties in experimental models of neurological diseases and cognitive impairment. Its activities seem to include a modulation of different cellular mechanisms related to neurons' survival, including mitochondrial function and autophagy, and the decrease of pathological alterations linked to cognitive impairment.

The activities of berberine have been studied in models of Parkinson's disease, especially in relation to mitochondrial dysfunction and defective autophagy [9]. Treatments with berberine improved mitochondrial function and modulated the processes of autophagy linked to neuronal injuries. Improvements in motor function were also found in the experimental model [9]. These data indicate that the of mitochondrial homeostasis and the normal activity of autophagy may be important underlying mechanisms of its properties.

Berberine hydrochloride has also been studied using a behavioral and an immunohistochemical approach in a rat model of methamphetamine-induced cognitive dysfunction [10]. Treatments have produced effects and an improvement in cognitive outcomes in experimental animals, thus further supporting that berberine may be for function under the conditions linked to cognitive impairment [10].

In sum, these studies indicate that berberine may have actions via multiple cellular mechanisms while helping to improve neurological and cognitive function. However, available mainly and further clinical studies are required to establish if similar actions are exerted in humans [9, 10].

2.5. Cardiovascular protective effects

Berberine has also been shown to have cardio-protective effects. Pharmacologic action could be linked to modulation of cellular processes underlying cardiac aging and senescence. Berberine may be shown in experiments to modulate cellular senescence signaling pathways.

The cardio-protective actions of berberine against senescence of the heart have been linked to modulation of the Klotho/SIRT1 pathway [11]. Klotho and SIRT1 have been shown to be linked with regulation of cell aging and promotion of normal functioning, suggesting that modulation of this pathway may contribute to the protective actions of berberine on the heart against damage [11].

Such evidence points toward a potential cardiovascular role for berberine that may be more than one based on regulation of the traditional metabolic factors and may involve a direct action through modulation of pathways linked with cardiac aging. Given that the evidence for this is experimental, however, further clinical studies will be required to establish the therapeutic relevance of such effects in humans.

3. Pharmacokinetic limitations and bioavailability

3.1. Poor oral bioavailability and intestinal absorption

The drawback of berberine is poor oral bioavailability. Berberine possesses a broad spectrum of activities, but the oral dose of the drug delivered to the systemic circulation is very low. The low

DOI: 10.54254/2753-8818/2027.MB38006

systemic exposure to berberine can be attributed to multiple pharmacokinetic barriers, such as poor solubility, low intestinal permeability, P-glycoprotein (P-gp)-mediated efflux, and high intestinal and hepatic metabolism [1, 2].

Berberine's low membrane permeability and poor solubility limit its potential to penetrate the intestinal epithelium [2]. Furthermore, berberine can be effluxed back by the P-gp to the intestinal lumen, which further limits berberine's systemic absorption. These are due to the exceedingly low oral bioavailability of berberine [2].

The significant role of the first-pass metabolism is further indicated by comparison between oral and rectal administration in rats. The difference in bioavailability between oral and rectal administration suggests that the intestinal and hepatic first-pass metabolism makes an important contribution to the low systemic availability of the drug after oral dose administration [12].

In summary, the oral bioavailability of berberine is affected by physicochemical and biological factors rather than a single aspect. Poor solubility, low intestinal permeability, P-gp-mediated efflux, and metabolism all contribute to reducing systemic exposure following oral dose administration [1, 2, 12].

3.2. P-glycoprotein-mediated efflux and metabolism

Transporter-Mediated Efflux and Metabolism: In addition to poor intestinal absorption, berberine's limited systemic exposure is mediated in part by transporters that can efflux (pump back into the intestinal lumen) and metabolize the compound. One such transporter is P-glycoprotein (P-gp), an efflux transporter expressed in the epithelium, which can limit the absorption of drugs by transporting them back into the intestinal lumen. Berberine is subject to this efflux, and thus P-gp-mediated efflux is another mechanism that can limit oral bioavailability [2, 13].

Comparisons of berberine with five other protoberberine alkaloids also revealed that the chemical structure can influence the P-gp-mediated efflux capability [13]. These data suggest that the structural features may impact the interactions of berberine-related compounds with the P-gp and help to clarify why the transporter-mediated efflux plays an important role in the limitation of the intestinal exposure.

The low systemic availability of berberine is also mediated in part by metabolism. Once berberine is absorbed, it may undergo significant intestinal and hepatic metabolism prior to systemic circulation [1, 2]. Thus, P-gp-mediated efflux and extensive metabolism collectively mediate the low systemic exposure of berberine after oral administration [2, 13].

Insight into these mechanisms is critical for the design of formulation and delivery strategies aimed at helping overcome the pharmacokinetic shortcomings of berberine.

3.3. Pharmacokinetics and tissue distribution

Berberine is characterized by low exposure in the systemic circulation and by its distribution in various tissues following administration. The plasma concentration of berberine may thus not adequately reflect its disposition.

Plasma pharmacokinetics and tissue distribution of berberine from different preparations of bile-processed Copitis Rhizoma have been examined in rats with type 2 diabetes [14]. Variations in pharmacokinetic profiles and tissue concentrations were noted among the various preparations examined. Bile-processed Rhizoma preparation was associated with higher concentrations in multiple tissues than those seen for berberine from other preparations, suggesting that processing methods may alter the systemic disposition and tissue distribution of berberine [14].

DOI: 10.54254/2753-8818/2027.MB38006

The distribution pattern of berberine is especially noteworthy in that low exposure of berberine in plasma cannot be linked to the lack of pharmacological activity. Absorption, metabolism, and tissue distribution all determine the availability of berberine, or of its metabolites, at various sites of action [1, 2]. Notably, after intestinal and hepatic metabolism, multiple berberine-derived metabolites are generated, and some metabolites retain biological activity. Low plasma parent-drug concentration does not rule out contributions from circulating metabolites or local intestinal pharmacological actions.

Taken together, the results of these animal studies suggest that the preparation and conditions for administration can impact the pharmacokinetic profile and its concentrations in the tissues [14]. These studies support approaches that would enhance its delivery to the relevant target tissues.

4. Strategies for improving berberine bioavailability

4.1. Structural modification of berberine

One possible avenue for enhancing the activity of berberine is through structural modification. Derivatives with biological activities could be designed by altering positions and/or functional groups of berberine.

Structural modification of berberine has led to novel derivatives of isoquinoline possessing varied antibacterial activities against phytopathogenic bacteria [15]. Some of them exhibited activity higher than the prototype compound, showing that alteration of molecular structure can have a significant impact upon biological activity [15].

Structure modification could also be pertinent to limitations in pharmacokinetic considerations, since molecular structure might be associated with the interaction with drug. Structural variation among berberine and other related protoberberine has been revealed to impact on P-glycoprotein-mediated efflux capacity [13].

In summary, structural modification offers an attractive way for the optimization of berberine-based compounds. However, the available reports do not provide direct evidence to the conclusion that the structural modifications studied in these antibacterial derivatives would be beneficial to the oral bioavailability [15]. It should be emphasized that these derivatives were primarily evaluated against phytopathogens; their performance for mammalian pharmacology and oral bioavailability remains untested. Further kinetic evaluation is thus necessary.

4.2. Nanoparticle-based delivery systems

Nanoparticles can offer an alternative approach for overcoming berberine formulation challenges. Nanoparticle encapsulation of berberine may yield benefits in terms of formulation stability and targeting.

Lactic-co-glycolic acid (PLGA) nanoparticles loaded with berberine have shown promise for the treatment of ulcerative colitis . The berberine-loaded nanoparticles showed improvement of ulcerative colitis by modulating theinterleukin-6 (IL-6)/interleukin-6 receptor (IL-6R) axis, suggesting that the PLGA nanoparticles are a viable system for berberine delivery [16].

The solid lipid nanoparticles have also been specifically designed for an improved oral delivery of berberine. The solid lipid nanoparticles of berberine were for an improvement of the conventional drug delivery and of its bioavailability [17].

As a whole, these reports show different nanoparticle systems have potential in the improvement of berberine delivery, and clinical studies are necessary for these systems to show consistently an

DOI: 10.54254/2753-8818/2027.MB38006

improvement in berberine exposure and therapeutic efficacy in humans [16, 17].

4.3. Novel physical formulation strategies

There are also some interesting new physical formulation strategies which can overcome the poor oral bioavailability of berberine. These strategies are different from the chemical modification strategy in that the physical form or the physical environment in which the drug is administered is changed to enhance absorption and systemic exposure.

Berberine LipoMicel, a new micellar berberine formulation, was investigated in a 30-day, randomized, crossover human study [18]. This new formulation combined berberine with an emulsified and microencapsulated matrix in hopes of enhancing bioavailability. There was an overall increase in systemic exposure relative to conventional berberine, which is promising for the success of micellar formulation in overcoming poor oral bioavailability [18].

This study has the significant advantage that the formulation was tested directly in human subjects rather than only in preclinical models. That being said, this study mainly looked at short-term pharmacokinetics, safety, and tolerability. Further research is required to assess if these increases in systemic bioavailability translate into better long-term therapeutic efficacy [18].

The micellar formulation of the drug shows promise as a physical formulation strategy for enhancing berberine delivery and offers valuable insight into further exploration of novel formulations for clinical use.

4.4. Absorption enhancement

A third strategy aimed at combating the low intestinal absorption of berberine is to try to augment intestinal absorption of the compound itself. As reduced intestinal permeation is also an underlying reason for its low bioavailability, the adjusting effect of absorption enhancers could possibly improve berberine intestinal transport.

The effects of the enhancer 1,2-distearoyl-sn-glycero-3-phososhoethanolamine (DSPE-PEG)polymer have been studied in rats [19]. The absorption was found to be increased in the small intestine, and the increased berberine transport through DSPE-PEG was linked to the paracellular pathway, indicating that DSPE-PEG is able to increase berberine transport through the space between neighboring intestinal epithelial cells [19].

According to the study, berberine transport was also increased by DSPE, and there were no signs of noticeable intestinal membrane toxicity [19]. This is an interesting observation, as an absorption enhancer that increases the intestinal permeability of berberine should not also cause the destruction of the intestinal barrier.

In summary, the absorption enhancement strategy seems to offer a straightforward means to increase berberine bioavailability, although the available data only concern a rat model and thus the efficiency and safety of this method need to be studied in humans [19].

5. Current research limitations

5.1. Limitations in mechanistic research

Despite the breadth of pharmacological effects attributed to berberine, its mechanisms of action are highly complex and poorly understood. Berberine has been reviewed as a multi-target therapeutic

DOI: 10.54254/2753-8818/2027.MB38006

drug. The multifaceted actions of berberine can affect a large number of molecular targets, signaling pathways, and biological processes.

The mechanisms of metabolic actions of berberine have been reviewed as a multi-target drug against obesity [20]. The pharmacological effects of berberine are not restricted to a specific molecular target but multiple biological processes, highlighting the intricate nature of its mechanism of action. Although considerable experimental evidence has pointed out some of the potential molecular pathways through which berberine exerts its effects, it is difficult to translate these mechanistic studies into a consistent body of clinical evidence [20].

A further limitation is that the mechanistic evidence is derived from a particular cell or animal model. These studies help to identify potential signaling pathways and may not fully reflect the action of berberine in humans.

In summary, the multi-target actions of berberine pose a challenge as well as a pharmacological advantage for mechanistic studies. More systematic investigations are required to establish the relationships among major targets and to understand which mechanism is most important in different disease conditions.

5.2. Limitations in clinical translation

Despite multiple strategies that have been explored for the enhancement of the pharmacologic outcome and bioavailability of natural bioactive substances like berberine, the translation of the research findings into clinical outcome is difficult.

The natural alkaloids research has emphasized the multi-target activities, pharmacokinetic issues, and the challenge of clinical translation [21]. Berberine is no exception to this general class of compounds, and the properties of berberine are an important challenge to its further clinical development [21].

The issue is particularly meaningful for the design of formulation approaches. Nanoparticle delivery systems, new physical formulations, and methods may enhance berberine delivery or systemic exposure under an experimental setup. Nevertheless, enhanced pharmacokinetic performance may not directly guarantee a long-term therapeutic effect or clinical outcome.

Consequently, a higher focus is required on human pharmacokinetic and clinical research to evaluate whether a promising delivery approach is able to offer meaningful and reproducible therapeutic gains.

5.3. Pharmacokinetic variability

The disposition of berberine might differ in different physiological and pathological conditions, and it is difficult to predict the exposure of berberine in the body and in different tissues. The factors affecting berberine disposition include intestinal absorption, metabolism, transporter-mediated efflux, and tissue distribution.

Pharmacokinetics and tissue distribution of total alkaloids of Corydalis saxicola Bunting have been studied in mice under various experimental conditions [22]. Berberine was one of the major bioactive alkaloids studied, and there were differences in pharmacokinetic behavior and tissue distribution between different physiological and pathological conditions [22].

The results indicate that factors related to disease might affect the disposition of the berberine-containing alkaloids. However, as it is a study in mice and it studies berberine in the berberine-containing mixture of alkaloids instead of isolated berberine in human participants, it could not determine the degree of interindividual pharmacokinetic variability in human participants [22]. It

DOI: 10.54254/2753-8818/2027.MB38006

should be noted that reference [22] investigated total alkaloid mixtures from Corydalis saxicola in mice, rather than purified berberine in human subjects; direct human evidence for interindividual variability of pure berberine remains scarce.

It is therefore necessary to conduct future studies in human participants to determine major factors that cause variability in berberine exposure, and their effect on the therapeutic efficacy of berberine.

6. Future perspectives

In future, efforts in berberine studies may further strive to clarify how the multiple pharmacological actions of berberine correlate to its pharmacokinetic behavior and therapeutic impacts. While multiple molecular targets and signaling pathways have been reported, our understanding of their significance and interplay remains incomplete [20]. A more systematic effort is needed to define the critical molecular targets and determine the reproducibility of mechanisms identified in cellular models and experimental animals.

Optimization of bioavailability-improving approaches for clinical translation is also an important future research direction. Strategies including structural modification, nanoparticle-based strategies, innovative physical formulations, and absorption enhancers show promise to improve berberine's pharmacological performance or systemic exposure [15-19]. However, many of these efforts are supported primarily by preclinical data. More emphasis should be placed on well-designed human clinical studies to assess safety, pharmacokinetic behavior, and therapeutic efficacy.

Understanding variability in berberine's pharmacokinetic behavior is also important. Physiological and pathological conditions could affect its absorption, metabolism, and tissue distribution, resulting in variable systemic exposure and therapeutic responses [22]. Human pharmacokinetic studies should characterize the major biological factors contributing to this variability and their influence on therapeutic outcomes.

In summary, future development of berberine should integrate mechanistic studies, pharmaceutical formulation, pharmacokinetic assessment, and clinical investigation. Strengthening the links between experimental evidence and human data will be critical in determining whether the pharmacological potential of berberine can be translated into robust therapeutic applications.

7. Conclusion

Berberine is a multitarget natural product with numerous biological properties. Its pharmacological activities include anti-inflammatory, antioxidant, metabolic regulatory, anticancer, neuroprotective, and cardiovascular protective effects. These activities have been related to the modulation of various molecular targets and intracellular signaling pathways. Despite this potential, its unsatisfactory pharmacokinetic properties limit its wider pharmacological application. Berberine exhibits poor oral bioavailability due to low solubility and membrane permeability, intestinal efflux, extensive metabolism, and complex tissue distribution.

Several methods have been explored to overcome these shortcomings. Structural modifications can alter the biological and pharmacokinetic behaviors of berberine derivatives. Nanoparticle-based systems and novel physical formulations, such as micellar formulations, may improve drug delivery and systemic exposure, while absorption enhancers may improve intestinal transport. However, most findings are from preclinical studies, and improved bioavailability does not necessarily ensure greater pharmacological efficacy in humans.

DOI: 10.54254/2753-8818/2027.MB38006

Another limitation relates to the multitarget pharmacological behavior of berberine, the challenge of translating delivery strategies into clinical use, and variability in its pharmacokinetic behavior. Further studies should combine mechanistic studies, formulation development, pharmacokinetic analysis, and well-designed human clinical trials. Overcoming these limitations would be essential to establish the clinical value of berberine and promote more effective and reliable therapeutic applications.

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