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Original Research Article

Novel drug delivery system of Chrysin in management and treatment of disease: An overview

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Abstract: ***Background:*** The pharmacological activities of chrysin, a naturally generated flavonoid, have been demonstrated to include anti-inflammatory in nature anticancer, and neuroprotective actions. Its quick metabolism, limited bioavailability, and poor water solubility, however, limit its prospects for clinical development. ***Objective:*** To explore and evaluate various novel drug delivery system (NDDS) approaches aimed at enhancing the pharmacokinetic properties, therapeutic efficacy, and target specificity of Chrysin. ***Discussion:*** The reviewed NDDS approaches not only enhanced Chrysin's pharmacokinetics but also facilitated targeted delivery and sustained release. Formulation challenges such as polymer compatibility, stability, and scalability, along with regulatory concerns, are discussed. The integration of nanotechnology offers promising potential for clinical translation. ***Conclusion:*** Chrysin, a natural flavonoid, has limitations in medical use due to poor solubility and quick breakdown. New delivery systems are being developed to overcome these issues. Chrysin, combined with certain compounds, is a more effective cancer treatment. Advanced formulations enhance its effectiveness, particularly for cancer, neurological disorders, and inflammatory diseases.

Keywords: Chrysin, pharmacokinetic parameters, application in NDDS, Marketed Formulation

INTRODUCTION

The development of innovative drug delivery methods (NDDS) are for herbal medications has received attention in recent decades. Ideally, the novel carriers should meet two key requirements. Firstly, the drug should be delivered at a rate that is directed by the body's needs, over the course of the treatment period. Secondly, the carriers should ensure that the active component of the herbal drug reaches the site ofaction[1].Recent advancements in(NDDSs) have garnered momentous attention due to their tangible benefits, including decreased dosing frequency, enhanced bioavailability, targeted site specificity, and reduced adverse effects[2].A new way of delivering medicine is being developed to fix the problems with the current method. This new approach targets the exact area of the body where the disease is and delivers the medicine directly to that spot. The goal is to give the right amount of medicine to the patient in a way that it reaches the part of the body where it's needed and starts working right away. This new system tries to avoid the problems with the old way of delivering medicine. There are several ways to achieve this new approach[3-5]. Chrysin is a common 15-carbon flavones found in various fruits, vegetables, and mushrooms, and it's considered a significant active compound. This compound is found in a wide variety of plant-based foods, where it plays a significant role in their nutritional and medicinal properties[6].Passion fruit (*Passiflora sp.),* honey, and propolis are significant natural sources of chrysin[7-10].Given blow are the various available sources of Chrysin in Fig 1.

Flavonoids, such as Chrysin is a group of plant chemicals that have been shown to be good for people's health. Because they have different effects on the body, such as reducing inflammation and protecting against cancer, they are used in many products like vitamins, medicines, and beauty products[11-14].Chrysin's high permeability and limited water solubility place it under Class II of the Biopharmaceutics Classification System (BCS). This classification indicates that the compound has limited ability to dissolve in water but can easily pass through biological membranes;Chrysin is a dietary Phytochemical that is a member of the flavones group, which is a subclass of flavonoids. It is sometimes referred to as 5,7-dihydroxyflavone or 5,7-dihydroxy-2-phenyl 4H-chromen-4-one. This classification is significant as it influences the compound's interactions with biological systems, which can affect its bioavailability and pharmacokinetic properties. The flavones category of flavonoids is characterized by the presence of a benzene ring and a heterocyclic ring, which contributes to the compound's unique properties and potential biological activities. Asflavonoids, Chrysin is a naturally occurring compound found in various plant-based foods and has been studied for its potential health benefits[15, 16]. Chrysin has been found to have various health benefits, such as reducing inflammation, fighting bacteria and viruses, lowering blood pressure, and preventing certain diseases like cancer and diabetes[17].

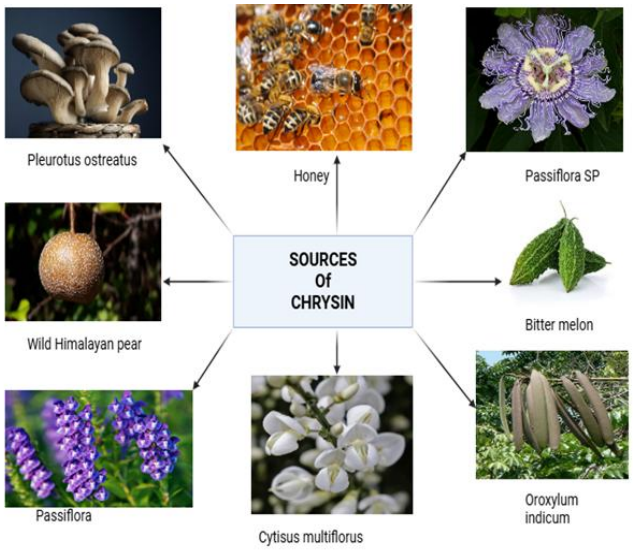

Fig 1: Various herbal sources of Chrysin

Pharmacokinetic Parameters

Table 1: Chrysin pharmacokinetic parameters

S.NO	ADME PARAMETER	DETAILS	REFERENCE
01	Absorption	Poor aqueous solubility & moderate permeability. Oral bioavailability < 1%: ~1% in rats; 0.003–0.02% in humans—plasma C_{max} 12–64 nm reported after oral dosing. Extensive first-pass metabolism in gut & liver. Low systemic levels due to rapid clearance.	16
02	Distribution	Limited central/peripheral exposure; accumulates mainly in GI tract enabling potential local effects in colon/ileum.	17
03	Metabolism	Extensively phase II metabolized by UGTs (especially UGT1A3/1A9/1A6/1A1/1A8/2B7/1A10) and SULTs to glucuronide & sulphate conjugates.Metabolites are substrates for efflux transporters (MRP2, BCRP), promoting elimination.>90% excreted via feces; minor urinary excretion of conjugates.	16
04	Elimination	Enterohepatic recycling may enhance local gut exposure. IV in rats: minutes. Oral in humans/animals: minutes to few hours	18
05	Half- life	Prodrug "C-1" (modified carbamate) extends $t_{1/2}$ to ~16.7 h (oral) and ~4.1 h (IV) with ~24% bioavailability in rats.	13

Bioavailability of Chrysin

In the human body, Chrysin is poorly absorbed into the body. It is rapidly broken down by the body's metabolic

processes and is quickly eliminated, which results in very low levels of the compound being available for use by the body[19].Chrysin undergoes metabolism primarily through conjugation reactions, including sulfation and glucuronidation, as well as to a lesser extent via oxidation in both intestinal and hepatic cells. Low concentrations of chrysene sulfonate and glucuronide have been detected in urine and plasma.During investigations on metabolism, the liver fluid of mice had the greatest concentrations of glucuronide and chrysin sulfate.The primary route for the removal of chrysin and its metabolites from the body is through faces[20].When a person takes a 400 mg dose of Chrysin orally, the amount of the flavonoid in their blood is very low. This is because it binds to other substances in the blood at a rate of over 99%. As a result, only a very small percentage, between 0.003 and 0.02%, of the Chrysin is absorbed into the body[19].The maximum plasma concentration of flavonoid aglycones is reported to be within a specific range of 12-64 nanomoles. This range indicates the highest level of these compounds that can be detected in the plasma after their absorption. The maximal amount of flavonoid cellulose in the blood is expected to be around 1 millimole / litre. This range suggests that the concentration of these compounds in the serum is relatively low compared to other substances. This is a relatively low concentration, which is why it's essential to administer Chrysin in a way that achieves serum concentrations within the micromolar range. Therefore, Chrysin should be administered to achieve serum concentrations within the micromolar series. This will ensure that the desired therapeutic effects can be achieved while minimizing potential side effects[21].

Application of Chrysin in Novel drug delivery system

Naturalistic products like propolis and honey that contain Chrysin have been used for a long time in traditional medicine and other products because they have good properties that help protect and heal.Passiflora, another important source of Chrysin, has been utilized in the treatment of insomnia resulting from neurological disorders[22].Nabavi et al. re-examined the roles of Chrysin and its derivatives in various neurological disorders, a move that is long overdue given the lack of comprehensive understanding in this area[23].This suggests that the potential therapeutic benefits of Chrysin in treating neurological disorders may be attributed to its ability to protect neurons from damage. As a result, the traditional use of plants containing Chrysin for this purpose may be based on its neuroprotective properties[15].

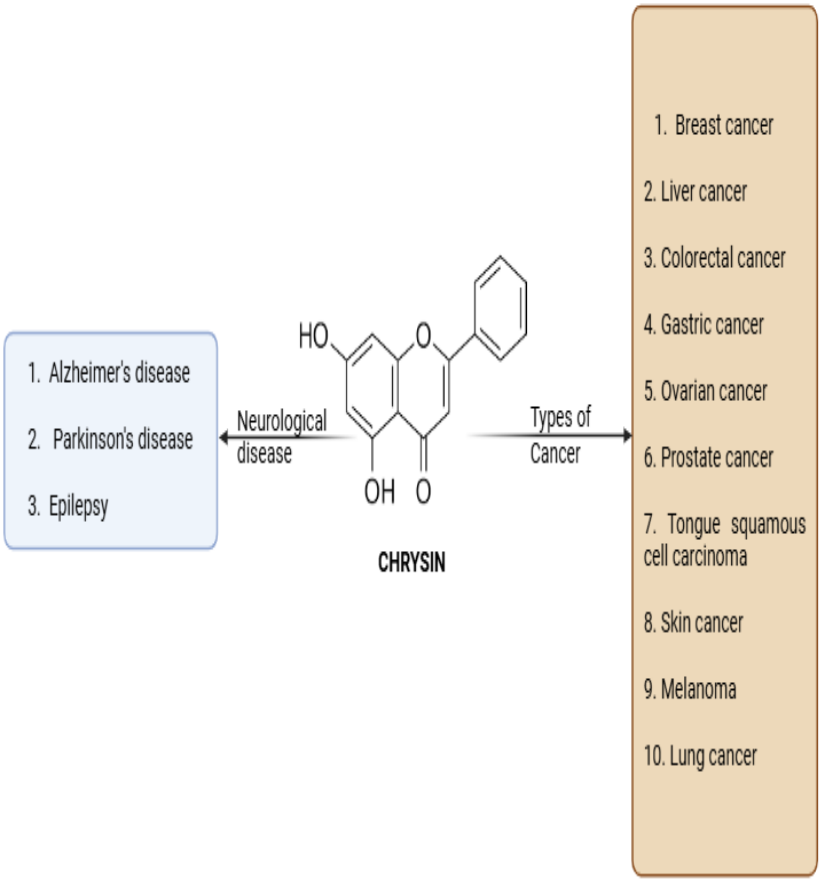

Fig 2: Different neurological disorders and types of cancer which can be cured by chrysin

Table 2: Chrysin used in different types of cancer

S. no	Types of Disease	Formulation	MOA	Findings	Reference
01	Breast cancer	Nanoparticle	Chrysin encapsulated with PLGA-PEG has a strong repressive impact on cell proliferation compared to chrysin alone, and PLGA-PEG is a viable strategy for breast cancer treatment.	In this work, anticipate that encapsulating chrysin with PLGA-PEG has a stronger impact on cell cycle arrest than pure chrysin and test the efficiency of chrysin loaded in PLGA-PEG in inhibiting cell proliferation and reducing cyclinD1.	24
02	Breast Cancer	Liposomes	-	In this work, CHR was encapsulated in liposomes utilizing the electrostatic deposition approach for protection and increased bioavailability.	25
03	Breast Cancer	Nano structured lipid carriers (NLCs)	Chrysin's molecular mechanism has yet to be established. Research found that chrysin suppressed cell proliferation in MDA-MB-231 via the PPAR alpha signal pathway.	In this study, used tiny lipid particles to carry a medicine called chrysin, which helps it be absorbed better and last longer in the area around cancer cells. The main goal of this research was to see how chrysin and these tiny particles affect cancer cells when given with a certain medicine, and also to understand how cancer cells grow and divide.	26
04	Breast Cancer	Micelle	-	In this study, a folate-conjugated Pluronic F127 (PF127) polymer was created with the capacity to form micelles that can encapsulate weakly water-soluble chrysin.	27
05	Liver cancer	Micelle	The Korsmeyer-Peppas model provided the best fit for the release kinetics of CHR from the CHR-M, suggesting that drug release occurred primarily through Fiskian diffusion. Notably, the CHR-M exhibited a significantly enhanced cellular uptake, with a five-fold increase compared to other formulations.	In this study, the characteristics of the micelles were studied. The micelles' ability to harm cells and be absorbed by cells was tested using human liver cancer cells.	28
06	Liver Cancer	Gold Nanoparticle	-	In this work, will report on the therapeutic efficacy of PEG-coated gold nanoparticles (GNPs) on two specific types of cancer cells: human hepG2 and mouse H22 hepatocellular carcinoma cell	29

				lines.	
07	Colorectal Cancer	Phytotomies	-	The firstaim of this study is to improve the pharmacokinetic and pharmacodynamic profile of chrysin by incorporating it into phytozoa form, as well as to characterize and pharmacologically evaluate anticancer activity of chrysin-loaded phytotomies for the treatment of colorectal cancer in Wistar rats.	30
08	Gastric Cancer	Nanoparticle	However, the molecular mechanism of chrysin is not well known and requires further investigation.	In this work, we investigated the effect of chrysin and its encapsulating form in PLGA-PEG-PLGA nanoparticles on gastric cancer cell lines.	31
09	Ovarian Cancer	Nanoparticle	-	In this study, discuss the current issues with Ova therapies, detail the numerous pathways involved in Ova drug resistance, and propose the use of nanotechnology and natural products to combat Ova drug resistance.	32
10	Prostate Cancer	Gold nanoparticle	The cellular uptake and radiosensitivity enhancement of gold-nanoparticles (GNPs) conjugated with glucose (Glu-GNPs) were evaluated and compared to those induced by GNPs conjugated with thiolategelatinesulphate (TGS-GNPs).	Used gold nanoparticles to make human prostate cancer cells more sensitive to radiation and to slow down their growth.	33
12	Skin cancer	Nanoemulgel	Creating skin-friendly and effective formulations is crucial. Using herbal ingredients in a way that takes advantage of their therapeutic properties allows for the development of non-toxic and non-irritating products. Researchers have successfully made and tested self-nanoemulsifying systems that contain chrysin for use in cancer treatments applied directly to the skin.	Study uses a scientific approach to test the effectiveness of a new way to deliver a plant-based medicine called chrysin to the skin to treat melanoma.	34
13	Melanoma	PLGA-PEG nanoparticles	-	Curcumin and chrysin were co-encapsulated into nanoparticles	34

				and their effects on the expression stages of key genes combined with tumor progression and metastasis, specifically MMP-2, MMP-9, TIMP-2, TIMP-1, and TERT, were examined in a mouse B16F10 melanoma tumour model.	

Table 3: Chrysin used in neurological diseases

S. no	Disease	Dosage form	Findings	Reference
01	Alzheimer	Solid Lipid nanoparticles	These findings suggest that chrysin's antioxidant and anti-inflammatory capabilities might help improve learning and memory deficits in rats injected with Aβ25-35.	36
02	Alzheimer	lipid-core nano capsules	The current investigation evaluated the effect of chrysin-loaded LNCs administration (for 14 days) on neurobehavioral changes in an AD model generated by intracerebroventricular (i.e.) Aβ injection in aged female mice.	37
03	Epilepsy	Poly (lactic-co-glycolic acid) nanoparticle	In this research shows that chrysin nanoparticles may help prevent epilepsy caused by kindling by reducing oxidative stress through a specific cellular pathway.	38

Table 4: Marketed formulation of Chrysin

S. no.	Composition	Brand Name (Company Name)	Reference
01	The provided compounds include Di-indolyl methane, Chrysin, and nettle root extract.	AE-3 (Pure Science)	39
02	Chrysin (5,7-Dihydroxyflavone)	Chrysin 500 milligram capsules, manufactured by Jarrow Formulas and based in the UK.	
03	The ingredients listed include purified water, Carthamus tinctorius seed oil commonly known as Safflower oil, Chrysin, Aloe barbadense commonly known as Aloe Vera gel extract, Seigel 305 which is a mixture of polyacrylamide, C13-14 isoparaffinic, and laureth-7, Potassium sorbate, and Sorbic acid.	Chrysin Cream (Naturally Complete, USA) Chrysin Cream is a topical product manufactured by Naturally Complete, a company based in the United States.	
04	The list of substances includes Chrysin, Vitamin D3, Balbina Metalepsis, Yohimbe Bark extract, Zinc, and Milk Thistle.	Chrysin 750 Capsules, a product by Gen X Labs, is A food additive designed to promote male health and testosterone levels.	
05	Chrysin	Chrysin powder obtained from Skin Actives Science, USA.	

Future Prospective of Chrysin

Flavonoids are presumed to be nontoxic due to their prevalent distribution in the diet with small scaleor no virulency. This property is noteworthy because many drugs used in the form of medicine have adverse side effects. The fact that flavonoids are widely consumed in food and beverages without causing harm to humans suggests that they are well-tolerated by the body. As a result, researchers and scientists are interested in studying the potential

health benefits of flavonoids, which may lead to the development of new, safer medications. Although chrysin has various uses and is available in commercial products, there is still a lack of knowledge about its effects on the body. To make sure it can be safely used in medical treatments, further studies are needed to understand its potential risks and side effects[39]. Future research should concentrate on the bioavailability aspects of chrysin and its derivatives. The use of nano-formulations may be beneficial in enhancing its bioavailability and pharmacokinetic profile. Prior to clinical applications of chrysin, further investigations into the molecular mechanisms underlying its metabolic and autoimmune inflammatory effects are highly desirable[40].

DISCUSSION

Chrysin, a natural flavonoid with potential health benefits, has limitations in medical use due to its poor solubility and quick breakdown in the body. However, new delivery systems are being developed to help overcome these problems and make chrysin more effective in treating various health issues.Chrysin is a more effective cancer treatment when it is combined with certain compounds. It can stop cancer cells from growing and cause them to die. These advanced formulations enhance chrysin's pharmacokinetic profile, improve target specificity, and boost its therapeutic efficacy, particularly for treating cancer, neurological disorders, and inflammatory diseases. The combination of chrysin with other compounds helps to increase its bioavailability and stability, allowing it to be more effectively absorbed and utilized by the body. This results in a more potent and targeted treatment, minimizing the risk of side effects and improving mostly treatment outcomes.The continued research and development of NDDS for chrysin not only opens new avenues for its clinical application but also contributes to the broader field of natural product-based therapeutics. Future efforts should focus on optimizing these delivery systems for largeproduction and regulatory approval to enable effectively translates from the laboratory to clinical practice.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable

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