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Comprehensive Review On Lipid Nanoparticles For Flavonoids Delivery

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ABSTRACT
The objective of this study is to examine the newest scientific developments concerning lipid-based nanocarriers, as indicated by recent pertinent literature. Lipid-based nanoparticles, including liposomes, niosomes, and micelles, are well recognized and FDA-approved. Lipid-based drug delivery facilitates the administration of natural phytoconstituents, as well as biopharmaceutical categorization system (BCS) class II and class IV pharmaceuticals, therefore enhancing their solubility, permeability, and bioavailability. Every formulation of lipid-based nanocarriers possesses distinct advantages and limitations. The SLN is an exceptional drug delivery method with extensive potential in the pharmaceutical sector. This study examines current advancements in solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and lipid drug conjugates (LDC) relevant to the administration of therapeutic agents, focusing on systems that have been tested and/or verified. This article reviews the current status of novel Nano delivery systems including nanospheres, nanocaspsules, micro- and Nanoemulsion, micelles, solid lipid nanoparticles and nanostructured lipid capsules, successfully developed for overcoming the delivery challenges of flavonoids

INTRODUCTION:

The sciences have been revolutionized by the rapid advancements in the production of nanoparticles that are uniform in size, shape, and composition. In recent years, there has been a surge in interest in the development of drug carriers that are based on lipids. The solid lipid nanoparticle is at the forefront of the swiftly evolving field of nanotechnology, with a wide range of potential applications in fields such as clinical medicine, research, drug delivery, and other sciences. Lipid nanoparticles present an opportunity to create novel therapeutics as a result of their distinctive size-dependent properties[1]. The capacity to incorporate drugs into nanocarriers provides a novel drug delivery prototype that has the potential to be employed for secondary and tertiary level drug targeting. As a result, solid lipid nanoparticles have garnered significant interest among researchers due to their potential for controlled and site-specific drug delivery. The novel drug delivery system provides a pathway to Nano/Micro formulation strategies that can address the obstacles associated with biopharmaceutical classification system (BCS) class II and class IV medications. Such medication or drug delivery targets the drug at the necessary site, albeit in a modest concentration, thereby enhancing therapeutic efficacy [2,3].

The novel drug delivery system comprises microparticles, nanoparticles, and dendrimers, as well as lipid-based liposomes, niosomes, phytosomes, micelles, hydrogels, quantum dots, and nanotubes. The particle dimension of Nanoparticulate drug delivery systems is between 1 and 100 nm. The development of a nanosized particulate system will enhance the transportation of drugs across the barrier. Nanomaterials are utilized extensively in diagnostic and therapeutic applications. Dior introduced liposomes to the cosmetic market in 1986, and they have been the only novel carrier system that has made a significant innovative contribution to the dermal area in the past 20 years. Liposomes were introduced to the pharmaceutical market after a

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delay of several years [4].

In addition to its technological advantages, the liposome garnered widespread public interest as a novel carrier. Microemulsions, multiple emulsions, and solid particles (e.g., microsponge delivery system (MDS) and thalaspheres) are among the numerous formulation principles that have been employed over the past two decades. Nevertheless, none of them were able to achieve a more widespread applicability for a variety of reasons, and none of them received the same level of attention as the liposomes. Solid particles offer certain advantages over liposomes and emulsions, such as the ability to regulate the release of the compound and the preservation of incorporated active compounds from chemical degradation [5]. Liposomes and emulsions are advantageous in that they are constituted of excipients that are well-tolerated and can be produced on a large scale, which is a necessary condition for the introduction of a carrier to the market. During the mid-1990s, various research groups concentrated on alternative nanoparticles composed of solid lipids, which are referred to as solid lipid nanoparticles (SLN, lipospheres, or nanospheres). The SLN minimizes the associated issues while combining the benefits of other innovative carrier systems (e.g., physical stability, protection of incorporated labile drugs from degradation, controlled release, outstanding tolerability) [6, 7].

SLN formulations have been devised and extensively characterized in vitro and in vivo for a variety of application routes, including oral, dermal, ocular, pulmonary, and rectal. An initial product, Nanobase, Yamanouchi, has been recently introduced to the Polish market as a topically applied emollient. At the turn of the millennium, the literature has been introduced to modifications of SLN, the so-called nanostructured lipid carriers (NLC), and the lipid drug conjugate (LDC) nanoparticles [8]. Conventional SLN's observed limitations are surmounted by these carrier systems. This paper aims to provide a concise overview of the various lipid-based carrier systems, including SLN, NLC, and LDC, as well as their structure and associated characteristics, stability, applied production methods, drug incorporation, and drug release mechanisms. A comprehensive review of the bioactivity of SLN following parenteral administration is conducted, including tolerability, toxicology, cellular absorption, albumin adsorption, pharmacokinetics, tissue distribution, and drug targeting [9, 10].

1 Novel Generation Of Lipid Nanocarriers:

1.1 Solid lipid nanoparticle (SLN)

Solid lipid nanoparticles (SLN) were created in the mid-1990s as an alternative carrier system to the extant traditional carriers, including emulsions, liposomes, and polymeric nanoparticles. Solid lipid nanoparticles (SLN) are colloidal drug carriers that are gaining attention. These SLN are prepared using either physiological lipids or lipid molecules that have a history of safe use in human medicine. They can be manufactured to integrate lipophilic or hydrophilic drugs under optimal conditions and appear to meet the criteria for an optimal particulate carrier system (11). The potential for a broad range of applications, the absence of organic solvents, the utilization of physiological lipids, and the established production method of high pressure homogenization are all advantages of SLN. Furthermore, the incorporation of poorly water-soluble drugs in the solid lipid matrix was claimed to result in enhanced bioavailability, protection of sensitive drug molecules from the outer environment (water, light), and even controlled release characteristics. The particle growth, unpredictable gelation tendency, inherent low incorporation rate, and unpredictable dynamics of polymorphic transitions are common disadvantages of SLN, which are a result of the crystalline structure of the solid lipid [12].

1.2 Nanostructured Lipid Carriers (NLC):

A new iteration of nanostructured lipid carriers (NLCs) has been created, which consists of a lipid matrix with a unique nanostructure. This nanostructure enhances drug delivery and securely embeds the drug during storage. The process of high-pressure homogenization can be used to produce these NLCs, and it can be modified to produce lipid particle dispersions with solid contents ranging from 30 to 80%. Carrier technology. Nevertheless, the NLC system mitigates or prevents certain potential issues that are linked to SLN (13). Mehnert and Mader emphasize the following aspects in their review:

- Pay-load for a number of drugs too low
- Drug expulsion during storage
- High water content of SLN dispersions.

Blending solid lipids with liquid lipids (oils) is a novel approach to the production of NLC, particularly when combining very distinct lipid molecules. In comparison to the original solid lipid, the resultant matrix of lipid particles exhibits a melting point depression; however, the matrix remains solid at body temperature. Different varieties of NLC are produced based on the composition of the lipid blend and the method of production. The fundamental concept is that the payload for active compounds is increased and expulsion of the compound during storage is prevented by providing the lipid matrix with a specific nanostructure [14-16].

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1.3 Lipid Drug Conjugates (LDC) Nanoparticle:

The limited capacity of SLNs to load hydrophilic drugs is a significant issue, as it is a result of partitioning effects that occur during the production process. The solid lipid matrix is capable of accommodating only hydrophilic drugs that are highly potent and administered at modest doses. This limitation has been addressed by the development of so-called LDC nanoparticles, which have drug loading capacities of up to 33%. The initial step in the preparation of an insoluble drug-lipid conjugate bulk is the formation of a salt (e.g., with a fatty acid) or covalently binding it to an ester or ether. The LDC is subsequently processed using high pressure homogenization (HPH) with an aqueous surfactant solution to produce a nanoparticle formulation. These matrices may have the potential to be used in the brain targeting of hydrophilic drugs in severe protozoal infections [17, 18].

2 Lipid-Based Delivery Systems For Flavonoids:

Plants serve as a primary source of pharmacologically active substances employed in the treatment of diseases throughout human history, resulting in the establishment of a medical field called herbal medicine. The findings indicate that two phenolic compounds, flavonoids and flavonolignans, exhibit C6-C3-C6 carbon structures. Flavonolignans consist of two components: flavonoid and phenylpropane. Flavonoids are categorized as a superfamily of polyphenols, consisting of seven distinct subclasses: flavones (e.g., tangeretin, luteolin, apigenin), flavonols (e.g., quercetin, kaempferol, myricetin, rutin), flavanones (e.g., hesperidin, hesperetin, naringenin), isoflavonoids (e.g., genistein, daidzein), anthocyanidins (e.g., delphinidin, pelargonidin, cyanidin, malvidin), flavan-3-ols (e.g., epigallocatechin, theaflavins, catechin, epicatechin gallate, proanthocyanidins, epigallocatechin gallate), and chalcones (e.g., flavokawain C, calomelanone, butein, homobutein, 4-hydroxychalcone, isoliquiritigenin) (19, 20). The previously listed examples are categorized as secondary metabolites, found in many plant parts, including flowers, fruits, roots, barks, grains, and stems. The specified classes of polyphenols exhibit significant anti-mutagenic, anti-cancer, antibacterial, antioxidant, antiviral, antifungal, and anti-inflammatory properties, making them promising candidates for the treatment of diverse cancers, neurodegenerative disorders, diabetes, cardiovascular diseases, and wound healing (Figure 1) (20).

Table 1 Features of nanoparticles as carriers for flavonoids.

Reference	Flavonoid	Nanoparticles in Whose Flavonoids are Encapsulated	Encapsulation Efficiency, %
Kumar R. and Abraham, 2017 (21)	Naringenin Flavanone 4, 5, 7 trihydroxyflavanone	Hybrid nanoparticles	99.93
J. Zhang et al., 2017 (22)	Apigenin Flavone 4′,5,7-trihydroxyflavone	Polymeric nanoparticles PLGA-PEG	56.6
Firouzi-Amandi et al., 2018 (23)	Chrysin Flavone 5,7-di-OH-flavone	Polymeric nanoparticles PLGA-PEG	88
Cherk Yong et al., 2019 (24)	Quercetin Flavonol 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one	Polymeric nanoparticles Chitosan-modified monoolein	99.4
Ouyang et al., 2019 (25)	Hesperetin Flavanone 3′, 5,7-trihydroxy-4 methoxyflavanone	Core-shell nanoparticles Hes Gd2(CO3)3@PDA nanoparticles	67.86
Pang et al., 2019 (26)	Kaempferol Flavonol 3,5,7-trihidroxi-2-(4-hidroxifenyl)-4H-1-benzopiran-4-ona	Inorganic nanoparticles Hydroxyapatite	90
Saha et al., 2020 (27)	Quercetin Flavonol 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one	Protein-based nanoparticles Albumin	89
Xu et al., 2020 (28)	Fisetin Flavonol 2-(3,4 dihydroxyphenyl)-3,7-dihydroxychromen-4-one	Nanoemulsion Emulsion with Miglyol® 812N/Labrasol®/Tween® 80/Lipoid E80®	-
L. Zhang et al., 2020 (29)	Baicalein Flavone 5,6,7-trihydroxyflavone	Polymeric nanoparticles Poly (ethylene glycol)-block-poly (D, L-lactide)	69.85
He et al., 2022 (30)	Quercetin Flavonol 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one	Complex coacervation-based nanoparticle system Carboxymethyl dextran, L-cysteine, and octadecylamine	72.13
Li et al., 2022 (31)	Baicalein Flavone 5,6,7-trihydroxyflavone	Core-shell nanoparticles Silica capped with poli disulfide	5.2
Mohamed et al., 2022 (32)	Naringin Flavanone (2S)-4′,5-Dihydroxy-7-[α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyloxy]flavan-4-one	Polymeric nanoparticles Dextrin	35

Rodrigues et al., 2022 (33)	Hesperetin Flavanone 3′, 5,7-trihydroxy-4-methoxyflavanone	Polymeric nanoparticles Ethylcellulose—PVA	-
Yang et al., 2022 (34)	Kaempferol Flavonol 3,5,7-trihidroxi-2-(4-hidroxifenyl)-4H-1-benzopiran-4-ona	Protein-based nanoparticles Fibroin	53.8
Krishnan et al., 2017 (35)	Hesperetin Flavanone 5, 7, 3′-trihydroxy-4′methoxy	Core-shell nanoparticles Au-mPEG (5000)	99
H. Zhang et al., 2017 (36)	Eupafolin	Polymeric nanoparticles Eudragit E100—PVA	-
vanden Braber et al., 2018 (37)	Genistein Isoflavone 4′,5,7-Trihydroxyisoflavone	Biopolymeric nanoparticles Chitosan with glucosamine hydrochloride	78
Bei et al., 2020 (38)	Wogonin Flavone 5,7-dihydroxy-8-methoxy flavone	Polymeric nanoparticles PLGA	74.89
Wang et al., 2020 (39)	Naringenin Flavanone (2S)-4′,5,7-Trihydroxyflavan-4-one	Natural product-based nanoparticles Rebaudioside A (steviol glycoside)	-
F. Zhang et al., 2020 (40)	Kaempferol Flavonol 3,5,7-trihidroxi-2-(4-hidroxifenyl)-4H-1-benzopiran-4-ona	Polymeric nanoparticles Polyvinylpyrrolidone (PVP)	-
Diez-Echave et al., 2021 (41)	Quercetin Flavonol 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one	Protein-based nanoparticles Silk fibroin	18.12
Al-Shalabi et al., 2022 (42)	Rhoifolin Flavone 7-[4,5-dihydroxy-6-(hydroxymethyl)-3-(3,4,5-trihydroxy-6-methyloxan-2-yl)oxyoxan-2-yl]oxy-5-hydroxy-2-(4-hydroxyphenyl)chromen-4-one	Polymeric nanoparticles PLGA followed by tannic acid-mediated surface modification with PEG	45
Tan et al., 2022 (43)	Luteolin Flavone 3′,4′,5,7-Tetrahydroxyflavone	Polymeric nanoparticles D-α-tocopherol PEG succinate-b-poly(β-thioester) copolymer	13.4

The extensive utilization of the previously mentioned families is hindered by several challenges, including inadequate water solubility, diminished membrane and intestinal permeability, low stability, susceptibility to degradation in highly acidic environments, rapid metabolism, and swift elimination from the bloodstream through immune response and renal clearance, notwithstanding their benefits [44, 45]. Various formulations have been developed to improve the bioavailability of the aforementioned substances, with the most notable being the use of nanomaterials as protected delivery vehicles. Nanotechnology and nanoscience constitute innovative and promising domains that provide a wide array of new applications and advanced technologies across several fields thanks to recent advancements[46].

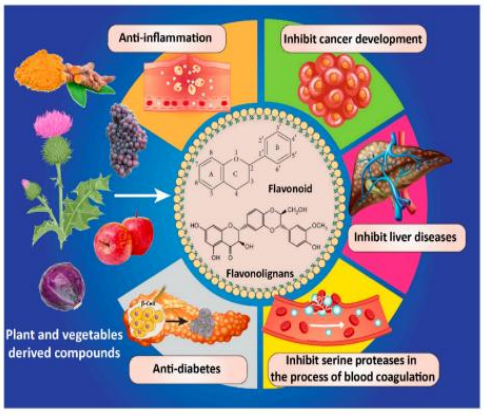

Figure 1 Different biological functions of flavonoids and flavonolignans

This is particularly applicable to environmental, biological, and biomedical domains. Reports indicate that employing nanoparticles for drug administration has several advantages, including targeted distribution, enhanced intracellular retention time, improved bioavailability, less side effects, and regulated release patterns. This study aims to evaluate recent advancements in formulation strategies that have enhanced the biological availability of flavonoids and flavonolignans. This text discusses lipid-based Nano delivery methods and their application for flavonoids and flavonolignans in medicines. The therapeutic applications, limits, and prospective future applications of lipid-based Nano delivery devices are further elucidated [47].

3 Advantages of Lipid Nanoparticles for Flavonoid Delivery:

3.1 Enhanced Solubility and Bioavailability:

In order to improve the solubility and absorption of flavonoids within the body, LNPs have the ability to encapsulate both hydrophilic and lipophilic flavonoids. Nanoparticles are utilized in the process of drug administration in order to dramatically boost the solubility and bioavailability of medications that are not easily soluble, which ultimately results in improved therapeutic efficacy [48]. In order to accomplish this, the particle size is decreased to the nanoscale, the surface area is increased, and the interactions between the medication and the solvent are improved. It is also possible to build nanoparticles in such a way that

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they prevent the drug from degrading and simplify the process of delivering the drug to specified locations within the body [49, 50].

3.2 Targeted Delivery:

LNPs can be designed to target specific tissues or cells, enhancing the therapeutic effect of flavonoids while minimizing side effects. One of the main advantages of nanomedicine could be its ability to deliver drugs at the targeted site. For instance, a nanoscale drug delivery system can specifically target cancer cells, preventing healthy cells from being eliminated. This process leads to lowering of side effects and increasing efficacy (51-53). Furthermore, the use of Nano-based drug delivery systems has significantly improved the drug's solubility, stability, and bioavailability. Nanoparticles could be designed to target specific cells or tissues, such as cells with malignant growth, and deliver drugs upon reaching the targeted sites. The unique size of nanoparticles and Nano devices and their ability to interact with biological systems at a cellular and molecular level enables the formulation of targeted therapy [54, 55].

3.3 Increased Stability:

LNPs protect flavonoids from degradation in the gastrointestinal tract and other harsh environments, increasing their stability and shelf life. Nanoparticles enhance drug delivery by improving stability, solubility, and targeted delivery, while minimizing side effects. They protect drugs from degradation in harsh environments, like the gastrointestinal tract, and ensure targeted delivery to specific sites. This leads to increased efficacy, reduced toxicity, and improved patient outcomes [56-58].

3.4 Controlled Release:

LNPs can be engineered to release flavonoids in a controlled manner, providing a sustained therapeutic effect. Nanoparticles can be designed to release their payloads in a controlled and sustained manner, ensuring a steady and effective concentration of the drug at the target site over time. This is especially important for chronic conditions or treatments that require long-term drug exposure [69, 60].

3.5 Improved Pharmacokinetics:

LNPs can modify the pharmacokinetic parameters of flavonoids, such as their absorption, distribution, metabolism, and excretion, leading to better therapeutic outcomes. The poor pharmacokinetic characteristics of most anticancer drugs have limited their clinical effectiveness. The application of nanoparticles as a novel drug delivery system has provided opportunities to tackle the current challenges facing conventional drug delivery systems such as poor pharmacokinetics, lack of specificity to tumour cells, multidrug resistance, and toxicity [61-63].

4 Application Of Flavonoids-Based Delivery Systems Towards Cancer Therapies

Cancer ranks as the second foremost cause of mortality globally. Cervical cancer is regarded as a significant affliction in low-income nations. The development of this cancer is mostly linked to persistent infection with the human papillomavirus. Despite the existence of preventive vaccines, their administration is predominantly confined to more developed nations, resulting in a significant proportion of unvaccinated women being particularly vulnerable to this malignancy. Current treatments rely on intrusive procedures and are markedly ineffective. Consequently, the pursuit of innovative, sophisticated, and individualized therapy strategies is essential [64-67].

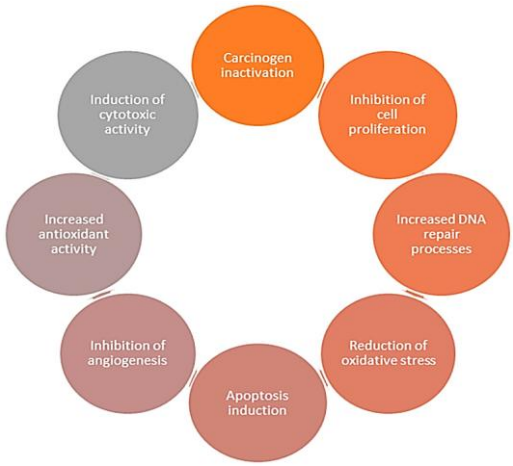

Figure 2 Schematic depiction of the primary mechanisms underlying the anticancer efficacy of flavonoids.

Flavonoids are a class of natural polyphenolic chemicals, renowned for their significant anticancer properties, hence holding potential for inclusion in cancer treatment procedures. Nonetheless, their application is constrained by their inadequate solubility, stability, and bioavailability. The encapsulation of flavonoids into delivery systems has emerged as an effective technique to enhance their stability and bioavailability, hence overcoming these constraints. This study aims to provide the most reliable flavonoid-based delivery systems created for anticancer medicines, highlighting advancements with a particular emphasis on cervical cancer treatment. The collected data demonstrated the significant therapeutic potential of flavonoids and underscores the importance of delivery systems, facilitating a deeper comprehension for future research on effective cancer treatment (68-70).

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4.1 The Role of Flavonoids in Apoptosis and Autophagy

Anticancer medicines aim to induce cancer cell death. Cancer cells avoid the apoptotic cascade, which prevents cell death. Inducing drug resistance helps tumor growth. Chinese medicine uses Vitex agnus-castus flavonoid cacticin as an anti-inflammatory. Casticin activates apoptosis via regulating Bcl-2 and other pro-survival proteins. This chemical induces intrinsic apoptosis in many cancer cell lines from various malignancies. This is done by downregulating Bcl-2, Bcl-xL, and survivin and upregulating Bax. Vitexin, a flavonoid extracted from Crataegus pinnatifida, kills cancer cells by reducing the Bcl-2/Bax ratio, mitochondrial cytochrome c release, and caspase-3 cleavage in human non-small cell lung cancer A549 cells[71-73].

4.2 Relationship between Flavonoids and Cancer Stem Cells:

Self-renewing and capable of both launching and maintaining tumor growth, cancer stem cells (CSCs) make up a minute but a crucial fraction of the tumor. In addition to being essential for the development of the disease, CSCs in cancer are also involved in its maintenance, progression, and metastasis. Emerging research suggests that flavonoids and other dietary phytochemicals can act as effective agents against CSCs. It has been shown, for instance, that naringenin, similar to hesperidin, suppresses breast cancer stem cells by elevating p53 and the estrogen receptor [74, 75].

4.3 The Role of Flavonoids in Cancer Cell Differentiation:

Differentiation therapy slows cancer cell proliferation by inducing differentiation. Differentiation therapy is less toxic than chemotherapy, reducing patient side effects. Quercetin and pelargonidin differentiate B16-F10 murine melanoma cells via transglutaminase type 2. Acute-promyelocytic leukemia (APL) patients often receive differentiation therapy, including all-trans retinoic acid (ATRA). Long-term treatment causes pharmaceutical resistance, requiring higher dosages (76-78). To counteract medication resistance, new drugs with stronger differentiation induction activity are needed. Flavonoids have several intriguing properties. Flavanoids differentiate APL cells. Flavone structure may be crucial for cell differentiation. Quercetin, apigenin, and luteolin stimulate APL granulocyte differentiation, while echinacea induces monocyte differentiation. However, galangin, kaempferol, and naringenin did not differentiate APL cells (79-81).

5 Future Challenges Of Nanomedicines:

There have been numerous advancements made in the field of nanomedicine, which demonstrate the significance of this topic in clinical and other medical application areas. In the course of their research, a great number of scientists have explored the relationship between nanomedicine and the treatment of cancers, as well as the reduction of mortality and morbidity rates [82-85]. There are, however, upcoming challenges that nanomedicines have been confronted with up until this point. The incorporation of nanomedicine into clinical practice will be met with a great deal of resistance from insurance companies, regulatory bodies, and professionals working in the public health sector. As of this moment, the Food and Drug Administration has not yet set any particular regulations for items that incorporate nanomaterials. These research projects are receiving less financing from the United States government agencies, such as the Environmental Protection Agency (EPA) and the National Institute for Occupational Safety and Health (NIOSH), respectively [86-90].

6 SUMMARY AND CONCLUSION

Flavonoids exhibit low bioavailability yet possess significant health potential that warrants investigation through enhanced medication delivery systems. The primary constraints for flavonoids in traversing biological membranes and achieving systemic absorption after oral administration are water solubility and stomach stability. Consequently, numerous outstanding bioactivities observed in vitro exhibit diminished or absent effects in vivo [91, 92]. Flavonoids delivered via Nano-sized devices exhibit significantly enhanced stability and absorption characteristics. As a result, the activity is augmented, more discernible, and extended. Compared to micro-delivery systems, nanocarriers offer several advantages: they exhibit greater stability, provide an increased surface area, and possess the potential to enhance bioavailability by improving absorption from enterocytes through receptor-mediated endocytosis, transcytosis, and phagocytosis via specialized microfold cells [93-95]. The Nano-delivery technologies enhance the regulated release of encapsulated flavonoids. All nanocarriers discussed in this review consist of substances approved as Generally Recognized As Safe (GRAS) and may serve as pivotal formulation carriers for novel and more efficacious functional foods, nutritional supplements, and herbal medical preparations [96-98]. The various techniques reported till today for formulation and evaluation of dosage forms as liposomes, niosomes, SLNs, nanostructured lipid carriers, Nano cholates etc. Novel formulations have advantages in both solubility and permeability enhancement of poorly

soluble drugs [99, 100].

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