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The Curcumin in the contemporary therapeutic modern world.

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Abstract:

The major polyphenolic compound of turmeric, curcumin, has a wide range of therapeutic properties, such as anticancer as well as neuroprotective, mainly by controlling major signaling systems. Nevertheless, its clinical translation is still poor, because its oral bioavailability is incredibly low, caused by poor aqueous solubility, rapid metabolism and rapid systemic clearance. This review brings out recent progress in nanotechnology-based delivery systems aimed to overcome these pharmacokinetic barriers. Special attention is given to polymeric nanoparticles and micelles to improve the solubility and cellular intake and the next generation liposomal platforms to enhance stability, allow a longer period of circulation, and promote controlled and site-specific delivery. The recent studies evidence shows the ability of these nanocarriers to enhance pharmacokinetic profile and in vivo therapeutic effect of curcumin significantly. Taken together, these developments make nanocarrier-based solutions one of the hopeful methods of converting curcumin into a promising therapeutic agent and out of a potent in vitro molecule.

Key Words: Curcumin, Bioavailability, Nanotechnology, Drug Delivery, Liposomes, Polymeric Nanoparticles.

الكركمين في العالم العلاجي الحديث

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مستخلص:

المركب الفينولي الرئيسي في الكركم، الكركمين، يمتلك مجموعة واسعة من الخصائص العلاجية، مثل مضادات السرطان وكذلك الحماية العصبية، principalmente من خلال التحكم في أنظمة الإشارات الرئيسية. ومع ذلك، لا يزال تطبيقه السريري محدودًا، due إلى انخفاض توافره الحيوي الفموي بشكل كبير، الناجم عن ضعف ذوبانه في الماء، التمثيل الغذائي السريع والإخراج الجهازي السريع.

تستعرض هذه المقالة التقدم الحديث في أنظمة التوصيل القائمة على تقنية النانو التي تهدف إلى التغلب على these الحواجز الدوائية الديناميكية. يتم إيلاء اهتمام خاص للجسيمات النانوية البوليمرية والمذيلات لتحسين الذوبان والامتصاص الخلوي، ومنصات الجسيمات الشحمية من الجيل التالي لتعزيز الاستقرار، وإطالة فترة الدوران، وتعزيز التوصيل المتحكم فيه والمحدد الموقع.

تظهر الأدلة من الدراسات الحديثة قدرة these الحوامل النانوية على تعزيز الملف الدوائي الديناميكي والتأثير العلاجي داخل الكائن الحي للكركمين بشكل ملحوظ. taken together، تجعل these التطورات الحلول القائمة على الحوامل النانوية one من الطرق الواعدة لتحويل الكركمين إلى عامل علاجي فعال من جزيء فعال في المختبر.

الكلمات المفتاحية: كركمين، توافر حيوي، تكنولوجيا النانو، توصيل الأدوية، جسيمات شحمية، جسيمات بوليمرية نانوية.

Introduction :

In this regard [1], the modern world views the great transformation in the context of integrative medicine and natural form of therapy. One of the most researching natural substances is curcumin [2]. It is not the extract of the rhizomes of the turmeric plant (*Curcuma longa L.*) itself, the pigment that is responsible in giving the spice its characteristic yellow colour but a latent treasure trove of pharmacy that has long been used in the traditional medical systems, namely in Ayurveda and Traditional Chinese Medicine [3].

Even with this excellent pharmacological profile, the therapeutic efficacy of curcumin is highly curtailed by its very low oral bioavailability [4]. The poor aqueous solubility, high rate of hepatic and intestinal metabolism, and low absorption among others are some of the factors that have been attributed to this fact [5]. These issues have led to a massive research to come up with new strategies that could be used to improve its delivery and effectiveness [6]. One of the outstanding developments is the thermo-nanoparticles liposom micelle and other novel complexes, e.g., curcumin- phosphatidylcholine (phytosomes) that has demonstrated remarkable increases in plasma curcumin levels [7]. New technologies like biopolymeric nanoparticles and exosomal carriers are another addition to the arsenal of successful curcumin delivery [8].

The present review, thus, seeks to offer the relevant and updated analysis of curcumin studies, which have appeared between 2020 and 2024 [9]. It sheds light on the molecular pathways that give rise to its biological effects, its multidrug potential and the new technological measures that are aimed at conquering its bioavailability constraints [10]. These discoveries provide new opportunities of converting this ancient natural compound to modern, effective, and clinically useful therapeutic agent [11].

Problem and Solutions: Biological issues and contemporary methods of getting over them --- The case of Curcumin.

Despite the high potential and high potential effect of curcumin, as being exhibited in the preclinical trial (in-vi-

tro and animal model), the most challenging issue in the application of curcumin in clinical practice and to attain the health effect of curcumin in human beings is the very low bioavailability of curcumin [12]. To define biological challenges and innovative strategies generated to combat the challenges, the following way might be used [13]:

One: biological Macro-challenges.

Absence of Aqueous Solubility: Curcumin is nearly insoluble in aqueous surrounding in the gastrointestinal tract which severely limits its dissolution and subsequent intake [14].

Ineffective Absorption: Curcumin does not get efficiently absorbed through the intestinal epithelial cells because its molecular size is relatively high, as well as is also hydrophobic [15].

Quick Metabolism: The curcumin is quickly and intensively metabolized in the liver (Phase II metabolism), intestinal wall where the curcumin is conjugated to curcumin glucuronide and curcumin sulfate [16]. Even the metabolites, in their turn, are far less biological in their activity compared to the parent compound [17]. Rapid Systemic Excretion: The body releases the bile and the metabolites rapidly within a very short duration of time leading to decrease in plasma half-life and increase of retention of the compound in the tissues within short period of time [18]. Stability Chemical Curcumin is highly unstable to alkaline environment (pH 7.0 or more) such as the small intestine and therefore rapidly decomposes to inactive compounds, such as ferulic acid and vanillin [19].

Second: Fresh Energizes to struggle against the Obstacles (Better Delivery Technologies)

In order to eradicate these issues, the present-day study (2020-2024) was planned on the basis of developing new delivery systems that will raise the level of the delivery pathway stability of curcumin into the organism and its protection [20]. Recent reviews have also summed up these more sophisticated delivery strategies and their effects on bioavailability and efficacy at length [21].

Polymeric Micelles and Nanoparticles: Micro view of Nano-Delivery Systems of Curcumin.

This form of systems is paradigm shift of delivery of such hard molecule as curcumin [22]. They are artificially produced nano-sized (typically 10- 200 nanometers) artificial products, which strive to address the inherent drawbacks of native curcumin [23].

1.1 Polymeric Micelles

Polymeric micelles refer to amphiphilic block copolymer formed nanostructure and that has a spherical shape [24]. These types of polymers have a characteristic hydrophobic (water-repulsive) and hydrophilic (water-attractive) part [25]. These polymers to be dissolved in water i.e. in the body fluids form a core-shell structure spontaneously [26]:

Hydrophobic Core: The hydrophobic part is agglomerated in the middle with a perfect pore to entrap and hold hydrophobic curcumin molecules [27].

Hydrophilic Shell(Corona): The outermost shell is made up of the segments that are water-loving followed by the fact that the entire micelle becomes soluble and stable in the blood [28]. It is also a shell that does not want to be recognized and destroyed rapidly by the immune system of the body, the so-called Stealth Effect, and such polymers as polyethylene glycol (PEG) usually help in it [29].

1.2 Mechanism of Action:

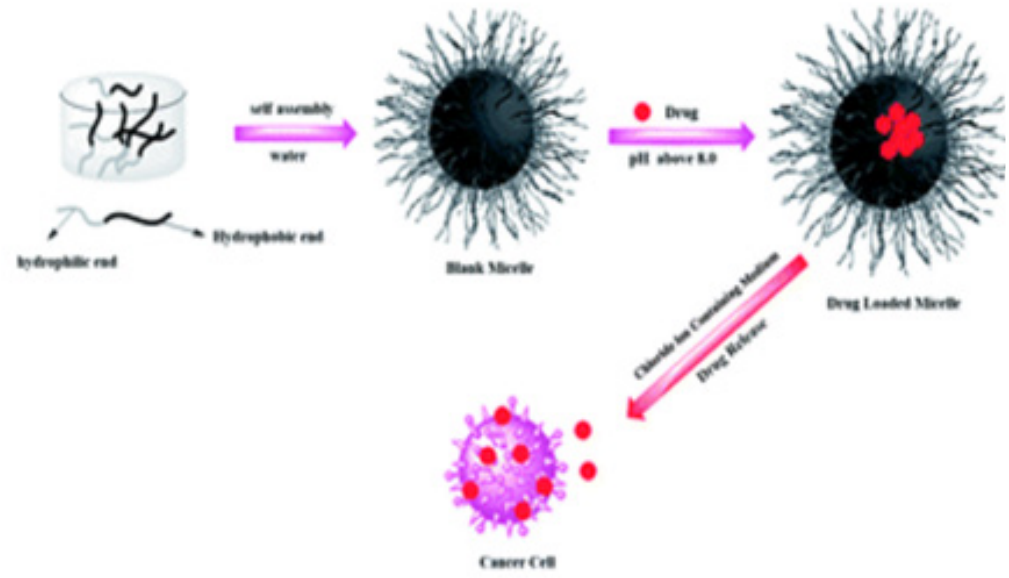
Solubilization: The concept behind this process is that it stabilizes curcumin, which is deposited to the hydrophobic core of the micelle and, therefore, the solubility of the hitherto insoluble compound in water is multiplied several times [30].

Protection: The curcumin is put around the core to prevent premature decadence in extreme alkalinity of the intestines [31].

Heightened Absorption: Mucus covering and the intestinal lining permit more correspondence and augmented absorption in the shell of the cells because it is small and hydrophilic [32]. This can be via the absorption of intact micelles into one of the enterocytes, or M- cells of the Peyer passages of the gut-associated lymphoid tissue (GALT) [33] **Fig(1):**

Passive Targeting due to the small size of the nanoscale, micelles can spe-

cifically target inflamed tissue or tumor via the Enhanced Permeability and Retention (EPR) effect in which the permeability of an extravasating and retaining inflamed tissue or tumor can allow extravasation and retention [34].



Fig(1): Polymeric Micelles

2- Polymeric Nanoparticles

Polymeric Nanoparticles are solid colloidal particles on which the curcumin is suspended, encapsulated or chemically bonded [35]. They are largely manufactured on using biodegradable/biocompatible polymers, Poly(lactic-co-glycolic acid) (PLGA) is the most studied and authorized by FDA [36].

There are two main types:

Nanospheres Curcumin: is uniformly dispersed on the polymer [37].

Nanocapsules: In this case the Curcumin is encircled in a liquid core (frequently an oil) and enclosed by a solid polymer shell [38].

2.1 Mechanism of Action:

High Payload and Sustained Release: Nanoparticles are able to deliver high concentration of curcumin [39]. Polymer matrix is viewed as a system whose structure holds curcumin inside the structure and prevents its diffusion out of the structure throughout a long period (days and even weeks) of time

through diffusion and gradual degradation of the polymer [40]. This will accommodate the problems of prompt eviction [41].

Cellular Uptake: Nanoparticles can readily find their way into the cell via endocytosis, a mechanism of cell delivery whereby the cargo is directly transported to the cell without necessarily using the cell surface P-gp efflux pumps [42].

Greater Physical and Chemical Stability: The solid matrix enhances physical and chemical stability of curcumin in it to that of the micelles [43].

Targeting Ability: Nanoparticles may be actively targeted (functionalized on the surface with targeting ligands such as folic acid expressed in the cancer cells, antibodies, peptides etc) to an area of interest of interest in the disease and minimise off-target effects [44]. Solid lipid nanoparticles (SLNs) are a potential subgroup of lipid-based polymeric systems, which improve physical stability and drug loading [45].

3- Liposomes Advanced Delivery Systems of Curcumin.

Liposomes form part of high-technology Multifunctional nanocarriers that have since become one of the most promising to overcome the significant bioavailability issues of curcumin [46]. They are designed on the particular constituents of biologic membranes therefore, they are very unique in drug delivery [47]. Recent researches are still working on improving their composition to be used in specific therapy [48].

3.1- The descriptive Structure and Composition.

Liposomes: These are self-forming, spherical vesicles, the characteristics of which consist of a phospholipid bilayer or a network of several phospholipid bilayers, as well as an aqueous core [49].

Phospholipid Bilayer: The structure of Membrane consists of amphiphilic phospholipids (e.g. phosphatidylcholine), a hydrophilic head group and tails that is composed of hydrophobic fatty acids [50]. These molecules will automatically fold within an aqueous

solution in a bid to safeguard the hydrophobic tails of the molecules in an effort to shield themselves around water as well as form a closed structure in a bilayer structure.

Aqueous Interior: This is what is of the liposome, which is filled with water [52].

3.2 Key Components:

Cholesterol: it is a vital additive that should be added to the lipid bi-layer [53]. It makes the membrane become bulkier to enhance the stability and removes the fluidity of the drug that is being encapsulated in the membrane and also removes the leakage of the drug [54]. It also leads to the rigidity of the liposome and this helps in the survival of the undesirable environment at the gastrointestinal tract [55]. The above may be reduced to a water soluble(hydrophilic) and fat soluble(hydrophobic) molecule to aqueous core and lipid bi-layer respectively [56].

Mechanism of Action: Liposomes may work by augmenting the transportation of Curcumin.

Solubilization and Protection: Curcumin is extremely hydrophobic, hence, it is absorbed to the hydrophobic segment of the lipid bi-layer readily [57]. This essentially renders the substance soluble in aqueous solution as well as averts its degradation in the alkaline PH in the intestine and metabolic enzymes [58].

Enhanced Cellular Absorption and Uptake: Liposomes enhance the absorption of curcumin in several ways [59]:

Fusion and Endocytosis: Fusion or Endocytosis may take place between the lipid based cell membrane of enterocytes (intestinal absorptive cells) to the liposomes or ingesting the liposomes intactly [60]. It is the direct delivery that circumvents a segment of the mechanism that prevents the absorption of free curcumin [61].

Lipidic Transport: Due to lipid structural composition, liposomes can enter into the lymphatic system where they escape the initial metabolism in the liver to some extent [62]. The consequence will be an increased amount of intact curcumin into the blood [63].

Sustained and Controlled Release: Liposome-based release of curcumin does not take place instantly [64]. It is a systematic procedure and this is

founded on:

3.3 Diffusion: between bi-layer of lipids.

Liposome Degradation: Myeloid destruction of the phospholipid membrane by enzyme (lipases) and degradation of the elements of the biological fluids [65]. Bilayer Composition: The fatty acids and cholesterol level to be used are to be optimised to reach the required bilayer fluidity and stability consequently determined the release rate and provided sustained release profile [66].

Passive and Active Targeting: The liposomes can be concentrated in the inflamed or cancerous cells as it has been observed in other nanoparticles by the Enhanced Permeability and Retention (EPR) effect [67]. Further, functionalization of the target cell surface with targeting ligands (anti bodies, peptides, folic acid), can be actively targeted to the target cells to become effective and minimises off-target responses [68].

4-PEGylated Liposomes (Stealth Liposomes).

Principle:These liposomes are coated with a synthetic polymer, which is Polyethylene Glycol (PEG) layer [69]. This process is known as PEGylation since a neutral cloud and hydrophilic one is formed on the surface of liposomes [70].

4.1 Mechanism and Benefits:

Less Opsonization and RES Clearance: PEG layer develops steric shield to decrease the binding of plasma proteins (opsonins) which would otherwise label liposome to be taken up by the Mononuclear Phagocyte System (MPS) the primary localization site of the immune system which occurs in most body areas, but is mainly in the liver and the spleen [71].

The reason behind the use of PEgylated liposomes of long circulation time is due to the fact that they are not degraded in blood too soon and results in a greatly increased half life [72]. Under this capability, it is possible to focus the ability to focus at higher levels at the focal point (e.g. a tumour) under the so called Enhanced Permeability and Retention (EPR) effect [73].

PEGylation to enhance Stability: PEGylation enhances the physical stability of liposomes as the aggregation is prevented during the storage and in

the bloodstream [74].

Implication to Curcumin: This is due to the fact that the Stealth property implies that a significantly higher percentage of the dosed curcumin gets to the diseased tissue and not to the liver [75].

4.2. Ligand-Targeted Liposomes

Principle: These are targeting liposomes whereby the targeting ligands are covalently conjugated to the liposome-surface (in PEGylated liposomes the ligands are generally conjugated to the far end of PEG chains) [76].

4.3 Mechanism and Benefits:

Specific Cell Recognition: The ligands are chosen due to their strong binding to surpass receptors on the target cell surface that are overexpressed (e.g., cancer cells, inflamed endothelial cells) [77].

Receptor-Mediated Endocytosis: once the target receptor has been bound to, the liposome is effectively endocytosed by the cell and its contents of curcumin are then directly released into the cytoplasm [78]. It circumvented efflux pumps, and provided elevated concentrations of intracellular concentrations [79].

The following evidence was used to show the presence of Targeting Ligands of Curcumin:

Folic Acid: Binds to folate receptor, which is over expressed in almost all the malignant diseases (e.g., ovarian, breast, lung) [80].

Transferrin: Binds to transferrin receptor that is over expressed in developing cells like cancerous cells due to the increased iron needs [81].

Peptides and Antibodies: There is the opportunity to specifically target it with peptides (e.g. RGD peptides to target integrin on the angiogenic vessels) or monoclonal antibodies [82].

Implication on Curcumin: Active targeting bestows a high degree of site-specificity of curcumin that augment its anti-inflammatory and cancer activities on the target site, and it circumvents the healthy cells and this will lead to minimum side effects [83].4.4. Smart Liposomes- Liposomes with Stimulus Adaptation.

Idea: These liposomes shall be stable during circulation but change their structure and de-load a cargo (curcumin) in a speedy sequence upon encountering a certain trigger at the destina-

tion of the disease [84]. Recent designs incorporate dual-responsive systems for more precise release [85].

4.5 Types and Mechanisms:

Trigger Microenvironment somewhat acidic (pH 6.5 -6.8) of tumors or even more acidic (pH 5.0 -5.5) of endosomes/lysosomes within cells [86].

Mechanism Add a pH-sensitive lipid (e.g., DOPE) or a polymer which remains stable in physiological pH (7.4) and which becomes destabilized, fuses or ruptures under acidic conditions to release curcumin to the point of need [87]. Such systems have shown promise in targeted anti-inflammatory and anticancer applications [88].

4.6 Enzyme-Sensitive Liposomes:

Stimulus: The increase of enzymes on a portion of the disease e.g. matrix metalloproteinases (MMPs) in cancer, phospholipases in inflammatory sites [89].

PEG conjugation with lipids is based on mechanism PEG which involves the use of peptide sequences that are cleavable by enzymes [90]. When it gets in touch with a specific enzyme, the PEG shield is removed, destabilising the liposome or revealing otherwise concealed targeting ligand [91].

4.7 Thermosensitive Liposomes:

Trigger: local low degree (external, e.g. 40-42degC) local hyperthermia of a tumor site [92].

Mechanism: Liquid-gel transition temperature is a specified temperature that is composed of lipids [93]. They are fixed in the body temperature and when exposed to minimal heating, through slight exposure, the bilayer leaks thus releasing the localized curcumin [94].

Table (1) Advanced designs not exhaustive Advanced designs are normally combined-e.g. to compose a PEGylated pH-sensitive, liposome functionalized with folic acid- to incorporate a multi-functional nanocarrier that can be circulated, tumor targeted and then effectively internalized by cancerous cells and after which releases its curcumin-cargo into the cell in response to the acid environment of the endosome [95].

Table (1) :
shows the state of art of delivery of curcumin.

Design	Key Feature	Mechanism of Operation	Benefit for Curcumin Delivery
PEGylated (Stealth)	Coating with Polyethylene Glycol (PEG) polymer	Creates a steric shield that avoids detection by the immune system (reduced opsonization), prolonging circulation time. Leverages the Enhanced Permeability and Retention (EPR) effect for passive tumor targeting.	Increases blood circulation half-life, allowing greater accumulation in target tissues like tumors.
Ligand-Targeted	Surface functionalization with targeting ligands (e.g., folic acid, antibodies)	Binds specifically to overexpressed receptors on target cells (e.g., cancer cells), facilitating receptor-mediated endocytosis.	Enhances cellular uptake in specific cells, increases therapeutic specificity, and reduces off-target effects.
Stimulus-Responsive	Incorporation of environment-sensitive lipids or polymers	Releases the encapsulated drug in response to specific internal triggers (e.g., low pH in tumors, elevated enzyme levels).	Provides spatiotemporal control over release, maximizing the local dose at the disease site and improving therapeutic efficacy.

Conclusions

To sum up, it could be said that the use of curcumin is a very promising natural product that has a strong therapeutic effect in a broad range of different diseases due to its multi-targeted molecular effects [96]. It however has a critical clinical translation issue, i.e. there is a latent pharmacokinetic challenge of low bioavailability [97]. Innovation of advanced nano-delivery plans especially the high-order delivery systems such as ligand-targeted liposomes and stimuli sensitive liposomes and polymeric nanoparticles have come out as the ultimate solution to the dilemma [98]. These technologies have been handy in enhancing the solubility of curcumin, inhibiting its degradation, improving its circulation, and directing it to specific tissues [99]. The following new modes of delivery are thus just around the corner of curcumin as a mainstream therapeutic agent [100]. In order to achieve the latter to the utmost, the scaling-up of the nanocarrier production, the extensive demonstration of their safety, and large-scale clinical trials should be taken into consideration in the work of the next generation [101]. Furthermore, exploring novel applications such as antimicrobial and wound healing therapies could broaden its clinical impact [102]. The interaction between the natural remedy that was present many centuries ago and the advanced nanotechnology has resulted in the creation of curcumin to transform it to become a safe, effective and reliable drug in the modern world [103].

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audience. Avoiding literal translations to keep the meaning intact would be crucial here.