Curcumin

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Natural products have been used in medicine for thousands of years, in the recent times they gained a significant popularity globally due to their potential health benefits.

Phytochemicals regulate differential gene expression to modulate various cellular pathways implicated in cellular protection.

Curcumin is a natural dietary polyphenol extracted from *Curcuma Longa L*. with different biological and pharmacological effects.

One of the important targets of curcumin is TLR-4, the receptor which plays a key role in the modulation of the immune responses and stimulate the production of inflammatory chemokines and cytokines.

Different studies have demonstrated that curcumin attenuates inflammatory response via TLR-4 acting directly on receptor, or by its downstream pathway.

Curcumin bioavailability is low, so the use of exosomes, as nano drug delivery, could improve the efficacy of curcumin in inflammatory diseases.

The focus of this review is to explore the therapeutic effect of curcumin interacting with TLR-4 receptor and how this modulation could improve the prognosis of neuroinflammatory and rheumatic diseases.

Curcumin, exosomes,TLR-4

1. Curcumin

The use of nutraceuticals, dietary supplements, and functional foods has been steadily gaining popularity due to the increased interest in natural products and their potential health benefits [6][7].

CUR (diferuloylmethane) is the principal Curcuminoid in turmeric, the Indian spice derived from the plant *Curcuma longa Linn* (family *Zingiberaceae*), and it is commonly used in the Asian continent, especially in India.

The IUPAC (International Union of Pure and Applied Chemistry) name of CUR is (1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, with a chemical formula of $C_{21}H_{20}O_6$ and a molecular weight of 368.38 g/mol. The chemistry of CUR is at the basis of its several biological activities. Indeed, its pharmacological effects are exerted by several functional moieties including phenolic hydroxyl groups, the central bis-α, β-unsaturated βdiketone, double-conjugated bonds, and methoxy groups [8].

CUR is hydrophobic as well as lipophilic, it has poor solubility in water or hydrophilic solutions, while it is highly soluble in organic solvents including methanol, ethanol, acetone and dimethyl sulfoxide [9]. It absorbs light, with a maximum wavelength of approximately 420 nm, which is what gives turmeric its yellow color [10].

The curcuminoid complex, found in the rhizome of turmeric (2.5–6%), contains CUR, demethoxycurcumin, and bis-demethoxycurcumin [11].

Polyphenols such as resveratrol and CUR, as well as flavonoids, were considered as the plant's defensive response against stress from ultraviolet radiation, pathogens, and physical damage. Resveratrol and CUR are anti-inflammatory, cyto- and DNA-protective, anti-diabetic, anti-cancer, and anti-aging dietary compounds [12][13][14][15][16]. These properties have been supported by several in vitro and in vivo studies and clinical trials [17][18][19].

The hydrophobic nature of CUR is responsible for its low water solubility and the rapid intestinal/hepatic metabolism limits its oral bioavailability, impeding clinical development of curcumin as a potential therapeutic agent [20].

The US Food and Drug Administration (FDA) have approved Curcuminoids as "Generally Recognized As Safe" (GRAS) [13], good tolerability and safety profiles have been shown by clinical trials, even at doses between 4000 and 8000 mg/day [21] and at doses up to 12,000 mg/day of 95% concentration of three curcuminoids: curcumin, bisdemethoxycurcumin, and demethoxycurcumin [22].

Clinicals studies further supported that a high single oral dose (up to 12 g/day) of curcuminoids were very well tolerated [14][23].

Several approaches have been used to increase the bioavailability of curcumin including liposomes, polymeric nanoparticles, micelles, extracellular vesicles and other formulations in order to identify drug vehicles; although, they are associated with inherent limitations, such as a short circulation time, as well as stability issues when used as unmodified liposomes in vivo [24][25].

Use of exosomes, as nano drug delivery vehicles, is an emerging area of research and has great potential for the development of novel therapeutic applications [26].

Exosomes are the smaller EVs, which contain different bioactive compounds with their cargo, which could lead to cell behavior changes in the recipient cell. Exosomes as drug carriers have the potential to overcome the limitations associated with other nanoparticle-based technologies [26][27].

There are several advantages of using exosomes as drug carrier systems, such as: low immunogenicity, biodegradability, non-toxicity, a strong cargo-loading and cargo protective capacity, marked ability to overcome natural barriers and penetrate into deep tissues [28], intrinsic cell targeting potential in native structure and deformable conformations [29], and marked ability to cross the blood–brain barrier (BBB) [30][31].

Exosomes contain also microRNA (miRNA), the small noncoding RNAs which act as epigenetic negative/positive regulators in various physiological processes [32][33].

A large number of studies have demonstrated that dietary compounds and bioactive foods could change the expression of various miRNAs involved in various well-known cancer processes such as angiogenesis, cell cycle regulation, apoptosis, differentiation, inflammation, metastasis, and pathways involved in stress response [14][34][35].

miRNAs are one of the important targets for CUR [36]. Several studies indicated that CUR could exert potential anti-cancer properties via targeting miRNAs, such as miRNA-34a, miRNA-21, miRNA-181, miRNA-7, miRNA-9, and miRNA-200c. Moreover, it has been shown that CUR could affect cell sensitivity to chemotherapy via targeting a variety of miRNAs such as miRNA-186, miRNA-21, and miRNA-27a [37][38].

2. Curcumin (CUR) and Exosomes

The efficacy of CUR is evidenced by different studies, most of them have involved animal experiments; however, there are several reports about the benefits of curcumin use in humans.

Into the body, the absorption of CUR is poor, and even when absorbed it is rapidly metabolized and excreted [39][40], moreover very high doses (>3.6 g/day in humans) are required to produce possible medicinal effect [41].

An appropriate drug delivery system is necessary for its clinical application, one of these is represented by extracellular vesicles (EVs), that carry a cargo of proteins, lipids, RNA, miRNA, and DNA. Due to their properties of shuttling in-and-out of the cells these particles have been exploited as a possible curcumin carrier [42].

EVs, heterogeneous membranous structures circulating in the extracellular body fluid, have a crucial role in cell–cell signaling representing one of the new emerging modes of cell communication. EVs are involved in many biological responses including inflammation and play a key role in a number of diseases, such as inflammatory bases neurodegenerative diseases and rheumatic diseases [43][44][45][46][47][48][49][50].

EVs are secreted from prokaryotic and a wide variety of eukaryotic cells types, and have been isolated in various body fluids from the main fluids in the organism [51][52].

Classification of the three main types of EVs is based upon performance and size: apoptotic bodies (up to 4000 nm in diameter) and microvesicles (100–1000 nm) are formed by outward budding of the plasma membrane, whereas exosomes are smaller in size (100 nm), are formed and stored within the cell before their release [53], and represent a new focus of research interest.

Among the EVs, exosomes gained a great attention for the delivery of natural compounds. Exosomes contain different bioactive compounds including protein, mRNA, miRNA [54] that, with their cargo, could lead to behavior changes in the cell recipient.

Exosomes could deliver their material to the designated cell recipient via receptor–ligand interaction, direct fusion of membranes, or internalization via endocytosis [55]. After internalization, exosomes may fuse with the limiting membrane of endosomes, resulting in the horizontal genetic transfer of their content to the cytoplasm of target cells. The bioactive molecules contained in exosomes have been shown to impact target cells via the following mechanisms: (1) direct stimulation of target cells via surface-bound ligands; (2) transfer of activated receptors to recipient cells; and (3) epigenetic reprograming of recipient cells via delivery of functional proteins, lipids, and RNAs [56].

Extensive data have shown the use of exosomes as vehicles for therapeutic drug delivery, having desirable features such as a long circulating half-life, intrinsic ability to target tissues, biocompatibility, minimal or no inherent toxicity issue, and are also employed to carry small molecular drugs across the BBB [30][57].

To load exosomes with active compounds, various methods were used, including simple incubation of exosomes and active compounds, sonication of a mixture of exosomes and active compounds, and electroporation of exosomes [31].

There are two major formulations of CUR and exosomes: (a) CUR encapsulated or loaded exosomes (exocur) prepared by loading CUR in the exosome, and (b) CUR-primed exosomes (CUR-EXO) when the cells are treated with CUR and then CUR-EXO are released [58][59][60][61].

Sun et al., for the first time, have shown the use of exosomes as a drug delivery system demonstrating that the anti-inflammatory activity of CUR with an exosomal formulation is remarkably higher when compared to liposomal CUR and free CUR [62].

In 2011, Zhuang et al. delivered CUR-loaded exosomes (ExoCUR) through a nasal route, and studied their effects on inflammatory diseases of the brain, founding a reduction in the number of inflamed microglial cells 2 h after administration, along with an increase of apoptotic events compared to a control group [63].

Kalani et al. administered CUR-loaded embryonic stem cell exosomes (MESC-ExoCUR) through the nasal route in ischemia-reperfusion (IR) injured mice and found that treatment with MESC-ExoCUR improved the stroke volume, ischemia-reperfusion injured neurons, brain vasculature, and vascular junction proteins. More interestingly, it has been shown an improvement in the neurological score after only 3 days of treatment when compared to IR-mice [60].

Emerging evidence has suggested that exosomes released by Human Umbilical Cord Mesenchymal Stem Cells contain miRNAs like let-7b [55].and miR-181c [64] that can specifically bind to the 3’ UTRs of target cellular mRNAs leading to the inhibition of TLR-4 expression and further to the suppression of the downstream NF-κB activity [65].

Aquin and coworkers incubated CUR with milk-derived exosomes and this formulation resulted with increase of 3-5 times in bioavailability of CUR in various organs versus free agent.

ExoCUR showed a significantly higher anti-inflammatory activity measured as NF-κB activation in human lung and breast cancer cells and antiproliferative activity against multiple cancer cell lines including, breast, lung, and cervical cancer [66].

To date, the existing literature does not report articles that consider the exact mechanism by which exosomes-CUR loaded modulate TLR-4 receptor, but surely, they are able to change the behaviour of recipient cell via targeting a sequence of cellular or molecular events associated with cell-signalling pathway.

Therefore, we could speculate that exosomes-CUR loaded may act on TLR-4 receptor by a direct stimulation of the receptor, by regulating target proteins in inflammatory signalling TLR-4 pathway, or by modulation of recipient cells miRNA.

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