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Lutein with various therapeutic activities based on micro and nanoformulations: A systematic mini-review

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ABSTRACT

Lutein is a carotenoid with reported anticancer, antibacterial, anticancer, antineurodegenerative, and anti-inflammatory activities. In addition, this bioactive phytocompound as a potential antioxidant has beneficial effects on cardiovascular, cognitive function, and eye health. Preserving neural efficiency, verbal fluency, and efficient learning have been identified for this metabolite. In the case of cardioprotective effect, lutein can increase nuclear factor erythroid 2-related factor 2 (Nrf2) and micro RNA (miR)-200a expressions. Lutein as a carotenoid is a natural lipid-soluble pigment, and its clinical application needs a new efficient formulation design suitable for physiological conditions. Nanoencapsulation of lutein by nanomaterials in different morphologies can ameliorate its therapeutic capacity by increasing bioavailability. This mini-review presents critical knowledge gaps in the clinical application of lutein and offers potential avenues for future research, particularly based on micro and nano aspects. In this regard, literatures were analyzed systematically from PubMed, which were published from 1994 to 2023. This mini-review showed that nanocarriers can increase the bioavailability of lutein in the liver and plasma compared to pristine lutein.

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Introduction

Lutein ($C_{40}H_{56}O_2$) and its structural isomer zeaxanthin as oxygenated carotenoid can be found in a variety of vegetables and fruits (Figure 1) [1]. A large body of evidence illustrates that this bioactive compound has various therapeutic activities including anticancer, antibacterial, anticancer, anti-neurodegenerative, and anti-inflammatory activities [2]. Moreover, this phytochemical compound has beneficial effects on cardiovascular, eye health, and cognitive function such as verbal fluency and efficient learning [3]. In the case of anticancer activity, lutein, a natural carotenoid, demonstrates an anticancer effect on non-small cell lung cancer (NSCLC) by targeting the ataxia-telangiectasia and rad3-related (ATR)/ checkpoint kinase 1 (Chk1)/p53 pathway. This metabolite induces cell cycle arrest and apoptosis, offering a new NSCLC treatment approach [4]. Lutein is a fat-soluble pigment and needs efficient formulations desirable for physiological conditions [5]. Increased bioavailability has been found for lutein loaded by drug delivery systems in micro and nanoscales [6]. In this way, nanoemulsion, solid lipid nanoparticle (NP), phospholipid micelle, liposome, polymeric NPs, and metal/metal oxide NPs may be used to load and encapsulate phytochemical compounds such as lutein. For example, an emulsion based on α-tocopheryl polyethylene glycol succinate with a size of 254.2 nm showed an increased level of lutein in the plasma and liver of the rodent model by 2- and 1.6-fold, respectively. As another example, chitosan NPs by a size range of 80–600 exhibited lutein levels in the liver, plasma, and eyes in mice by values of 53.9%, 54.5%, and 62.8%, respectively [7]. According to the above introduction, in this mini-review, literature about antioxidant, anti-inflammatory, antibacterial, anticancer, cardioprotective, and neuroprotective effects of lutein was analyzed systematically from PubMed, which were published from 1994 to 2023. In addition, we discussed novel designing of micro and

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nanoformulations of lutein with these therapeutic activities.

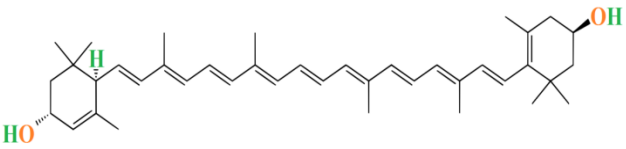


Fig. 1. Chemical stricture of lutein carotenoid.

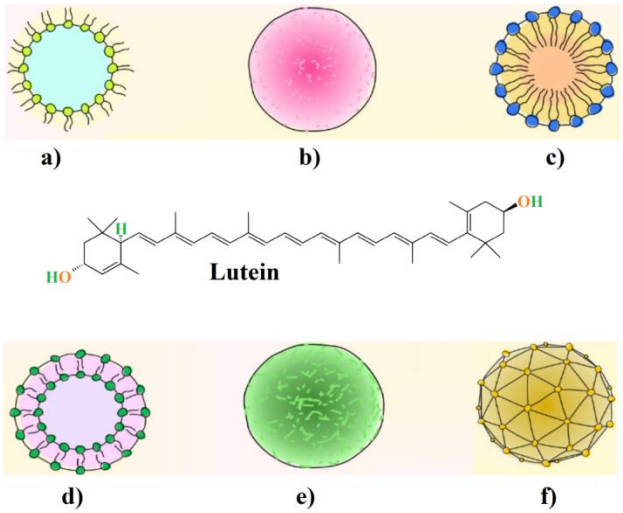


Fig. 2. Schematic image of various micro and nanocarriers including a) nanoemulsion, b) solid lipid NP, c) phospholipid micelle, d) liposome, e) polymeric NP, f) metal/metal oxide NP for loading lutein (adopted and modified from [8]).

Materials and methods

Search strategy

Scientific literatures were analyzed systematically from PubMed, which were published from 1994 to 2023. Several keywords including "lutein", "lutein AND antioxidant AND anti-inflammatory", "lutein AND antibacterial", "lutein" AND "anticancer", "lutein AND cardio AND cardiovascular", "lutein AND neuroprotective", and "lutein ANA nano" were selected for this study (Figure 2a-g).

Results and discussion

Antioxidant and anti-inflammatory effects

The number of publications per year showed an increasing trend from 1989 until 2023. The highest number of studies has been done in 2012 and 2022 by 27 publications (Figure 2a). Aging and many metabolic diseases, specifically type 2 diabetes and degenerative diseases such as Alzheimer's disease can be caused by oxidative stress of reactive oxygen species (ROS) activating inflammatory mediators. Lutein is a powerful antioxidant that defends the body against free radicals by quenching and scavenging free radicals. IL-6 expression in the retina and the activated signal transducer and activator of the transcription 3 (STAT3) signaling pathway are hindered by lutein [9]. As mentioned in the introduction section, nanomaterials (NMs) of different sizes and morphology may be employed for loading and encapsulation of therapeutic agents or drugs [10, 11]. Copolymers of poly (lactic-co-glycolic acid) (PLGA) with phospholipid were used for loading lutein and improving its bioavailability. For lutein-PLGA nanocarriers + phospholipid, bioavailability levels of lutein in the retina and serum were higher than lutein-mixed micelles and the lutein-PLGA without phospholipid with values of 365.2 % and 265.5 % respectively [12]. As mentioned in the introduction section, polymeric, metallic, and lipidic NPs are the main NMs to encapsulate and load therapeutic phytocompounds [10, 13]. In the case of polymeric NPs, polymer materials including chitosan, cellulose, and lipids can be employed for the passive delivery of lutein to the brain, eye, liver, and plasma by crossing the blood-retina barrier (Figure 3) [14].

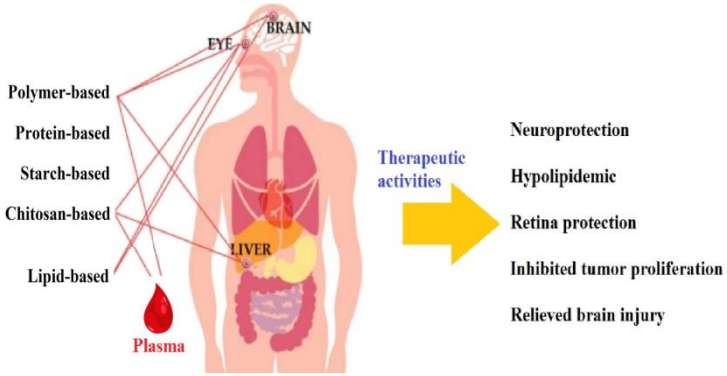


Fig. 3. Loading of lutein polymer-based, lipid-based, and natural products-based materials for passive targeting of plasma, liver, eye, and brain (Adapted and modified from [14]).

Antibacterial effect

The maximum number of publications (48) was found in 2022 for "antibacterial" and "lutein" words. Lutein can have antibiofilm and anti-quorum sensing activities against bacteria. Eradication of biofilm formation by *Pseudomonas aeruginosa* is a pivotal issue because these bacteria lead to the escalation of diabetic foot ulcer (DFU). Lutein isolated from *Chlorella pyrenoidosa* in a concentration of 20 µg/mL

exhibited the highest hindering and damaging of biofilm formation and pyocyanin production in *P. aeruginosa* PAO1 strain. During biofilm formation, RhlR, RhlI, LasI, and LasR contribute to the quorum sensing mechanism. A molecular docking study illustrated that lutein can interact with these proteins. In addition, gene expression of rhl and las was downregulated under different amounts of lutein [15]. The biodegradable film of cress seed mucilage was modified by lutein, maltodextrin, and alumina to enhance mechanical and antibacterial properties. The surface cracks of mucilage film were augmented by lutein. This modified film exhibited 23 and 26 mm inhibition zone diameters (IZDs) against to *Escherichia coli* and *Staphylococcus aureus*, respectively [16]. Isolated lutein from *Melhania zavattarii* Cufod leaves showed antibacterial activity against *E. coli*. The molecular docking study exhibited a binding energy of −7.05 kcal/mol towards peptide deformylase compared to chloramphenicol and β-amyrin palmitate with binding energy values of −6.87 and −9.09 kcal/mol, respectively [17].

Anticancer effect

In 2021, there were 64 publications on "lutein AND anticancer" (Figure 2d). Apoptosis in A549 human non-small-cell lung cancer cells has been induced upon lutein treatment via hindering the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) signaling pathway [18]. In a comparative study, lutein compared with astaxanthin and β-carotene carotenoids demonstrated remarkable anti-breast cancer activity via caspase-independent cell death and promoting cell-cycle arrest. In triple-negative breast cancer (TNBC) cells, there was augmented intracellular ROS generation as the main anticancer mechanism of lutein [19]. As a polymeric nanoformulation, lutein has been encapsulated into PLGA-polyethylene glycol (PEG) nanopolymers with a spherical shape and average size of 200 nm. These nanoformulations showed controlled sustainable release up to 72 h and higher antiproliferative activity with IC_{50} value of 10.9 µM compared to pristine lutein with IC_{50} value of 25 µM [20].

Fe_3O_4 NPs have been used for active targeting of cancer cells by their potential magnetic property. As an example, chitosan/alginate-coated Fe_3O_4 NPs were employed as the polymeric nanocarrier for loading lutein metabolite against breast cancer cells [21]. The development of selective, safer, and stronger anticancer therapies has been made possible by the numerous cancer remedies with associated restrictions and side effects. In this regard, several human cancer cell lines, including MCF-7, HepG2, A549, PC3, HCT116, and normal HFB4 cells, were tested for their cytotoxicity and biocompatibility [22]. The lutein compound was found to have significant anticancer activity against MCF-7 and HepG2 cells. The plant extract containing lutein was found to be a potent anticancer agent with an IC_{50} value of 3.10 µg/mL, which is close to that of the standard drug doxorubicin in MCF-7 cancer cells (IC_{50} 2.90 µg/mL). Additionally, a moderate effect was observed on HepG2 cells with an IC_{50} value of 6.11µg/mL versus 2.90µg/mL for doxorubicin. In contrast, the lutein-rich extract was inactive against A549 cells, PC3 cells, and HCT116 cells. Based on these findings, lutein appears to be a more promising anticancer agent than doxorubicin when it comes to MCF-7 cells, but further research is needed to determine its effectiveness against other types of cancer cells [22].

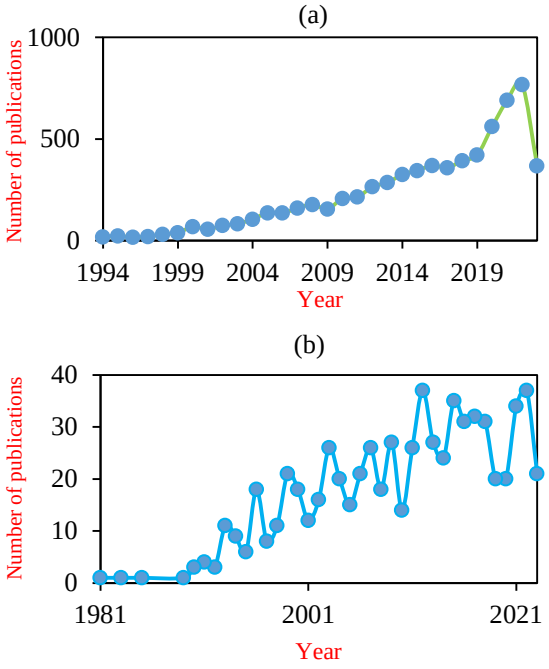
Cardioprotective effect

There were more publications in 2016, 2019, and 2021 in the year range of 1951-2023 (Figure 2e). Cardiometabolic health has been found for a higher dietary intake of lutein due to its antioxidant effect [23]. Isoproterenol-induced cardiac failure in the rat model can be protected upon lutein treatment by positively regulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/HO-1 signaling pathway. Antioxidant status and cardiac morphology have been ameliorated by this carotenoid [24]. Angiotensin II causes cardiac remodeling by promoting hypertrophy of cardiac myocytes and changes in cardiac fibroblast interstitial fibrotic. Lutein can decrease angiotensin II-induced interleukin-11 (IL-11) expression [25]. In the case of an experimental model of isoprenaline-induced myocardial infarction, lutein can reduce serum creatine kinas-MB activity, restore ejection fraction, and ameliorate QRS and QTc intervals compared with the control group. Pretreatment of this animal model by lutein led to downregulation of thioredoxin-interacting protein (TXNIP), long noncoding MI associated transcript (lncRNA MIAT), and increase of Nrf2 and

micro RNA (miR)-200a expressions compared with the control [26].

Neuroprotective effect

The highest number of publications (10) were found in 2021 (Figure 4f). Degradation of rhodopsin (a light-sensitive protein) is prevented and the survival rate of photoreceptors is increased by lutein. Opsin expression in cone cells and rhodopsin expression in rod cells have been augmented under the effect of this metabolite [27]. Synaptophysin, a synaptic vesicle protein, may be preserved by lutein [9]. In this way, the subsequent synaptophysin reduction, the brain-derived neurotrophic factor (BDNF) depletion, and activation of extracellular signal-regulated kinase (ERK) in the diabetic retina model were hindered by lutein. The metabolic status of the diabetic mice has not affected by lutein. However, the visual impairment (diabetic retinopathy) and ROS production in the retina have been inhibited by lutein [28]. Epilepsy as one of the major neurological disorders results from oxidative stress [29]. The toxic effects of sodium valproate, a common antiepileptic drug for the treatment of epilepsy, have led to clinical limitations of this drug. Lutein in combination therapy with sodium valproate decreased serum tumor necrosis factor-alpha (TNF-α) level, oxidative stress in hippocampal homogenate, and cerebral injury in the pilocarpine-induced epileptic rat model [30].



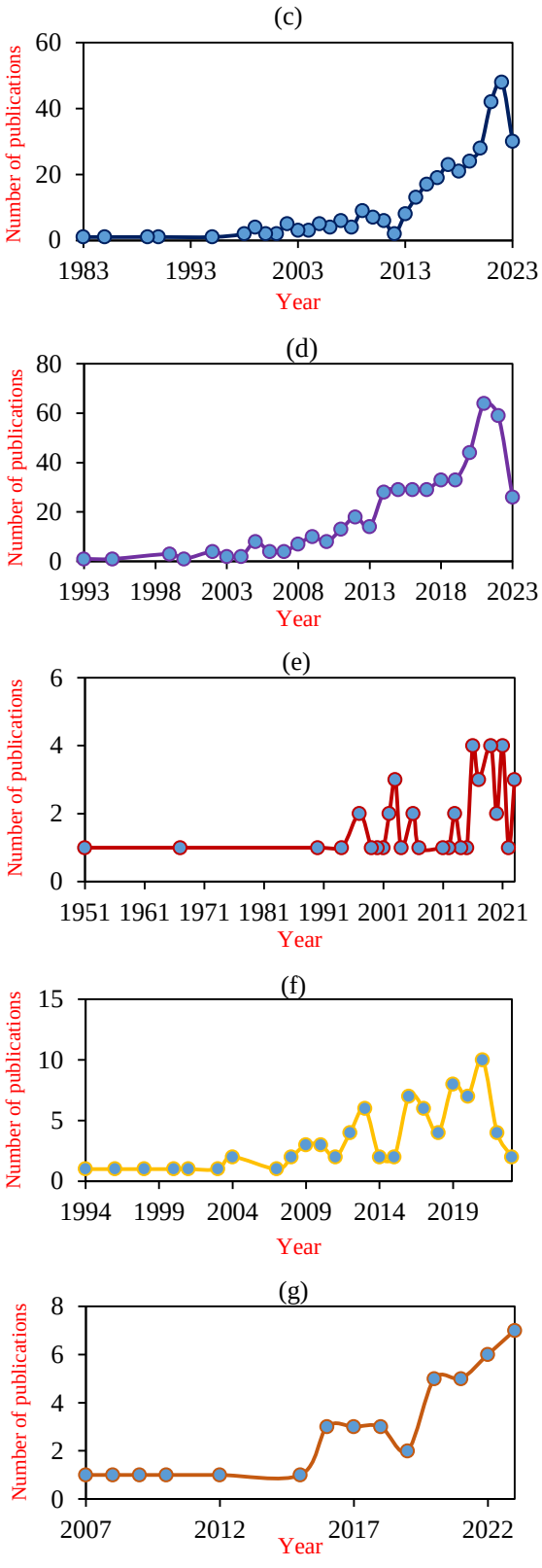


Fig. 4. Number of publications per year in the search range from 1994 to 2023. Search keywords were "lutein" (a), "lutein AND antioxidant AND anti-inflammatory" (b), "lutein AND antibacterial" (c), "lutein AND anticancer" (d), "lutein AND cardio AND cardiovascular" (e), "lutein AND neuroprotective" (f), and "lutein ANA nano" (g) (Source: PubMed).

Conclusions

A combination of lutein with conventional antibiotics such as azithromycin can hinder and eradicate biofilm formation in DFU caused by *P. aeruginosa*. Lutein inhibits the degradation of rhodopsin and causes the survival rate of photoreceptors. A low risk of coronary heart disease has been found for high blood concentrations of lutein metabolite. Pretreatment of an experimental model of isoprenaline-induced myocardial infarction by lutein results in downregulation of thioredoxin-interacting protein TXNIP, lncRNA MIAT, an increase of Nrf2 and miR-200a expressions compared with the control. Lutein in combination therapy with sodium valproate decreased serumTNF-α level, oxidative stress in hippocampal homogenate, and cerebral injury in the rat model. As the main conclusion, nanocarriers with unique physicochemical properties in the nanoscale can ameliorate the bioavailability of lutein in physiological conditions. Increased level of lutein in the plasma and liver has been indicated for drug delivery systems in the nanoscale.

Study Highlights

- A combination of lutein with conventional antibiotics such as azithromycin can hinder and eradicate biofilm formation in DFU caused by *P. aeruginosa*.
- Lutein inhibits the degradation of rhodopsin and causes the survival rate of photoreceptors.
- A low risk of coronary heart disease has been found for high blood concentrations of lutein metabolite.
- Lutein in combination therapy with sodium valproate decreased serumTNF-α level, oxidative stress in hippocampal homogenate.
- Nanocarriers with unique physicochemical properties in the nanoscale can ameliorate the bioavailability of lutein in physiological conditions.
- Increased level of lutein in the plasma and liver has been indicated for drug delivery systems in the nanoscale.

Abbreviations

ATR: Ataxia-telangiectasia and rad3-related
BDNF: Brain-derived neurotrophic factor
Chk1: Checkpoint kinase 1
DFU: Diabetic foot ulcer
ERK: Extracellular signal-regulated kinase
IL-11: Interleukin-11
IZDs: Inhibition zone diameters
lncRNA MIAT: Long noncoding MI associated transcript
miR: Micro RNA
NMs: Nanomaterials
NP: Nanoparticle
Nrf2: Nuclear factor erythroid 2-related factor 2
PEG: Polyethylene glycol
PI3K: Phosphoinositide 3-kinase
PKB: Protein kinase B
PLGA: Poly (lactic-co-glycolic acid)
ROS: Reactive oxygen species
STAT3: The activated signal transducer and activator of transcription 3
TNBC: Triple-negative breast cancer
TNF-α: Serum tumor necrosis factor-alpha
TXNIP: Thioredoxin-interacting protein

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

All authors: conceptualization, preparing the first draft, and editing.

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