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Research Article

Advances in Nanodelivery Approaches for Black Cumin (Nigella sativa) and Its Bioactive Constituents: A Comprehensive Review

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ABSTRACT

Nigella sativa belongs to the family of Ranunculaceae, it is commonly known as Black Cumin in English and Kalonji in Indian vernacular. Since time immemorial, it has been useful in Unani, Ayurveda and Chinese system of medicines. Thymoquinone, dithymoquinone, thymol, thymohydroquinone and nigellone are the main active constituents of the same. The therapeutic effect and bioavailability of extract and thymoquinone are restricted due to poor solubility and stability issues. Currently, researches have been carried out for the improvement of bioavailability of plant extract and their phytocompounds through nanotechnological approaches. The nature of the material used (PLGA, chitosan, cyclodextrins, etc.) for the preparation of nanoformulations have significant impacts on improving pharmacodynamics and pharmacokinetics of phytoconstituents. This review focuses on the aspects of nano formulations for delivery of Kalonji and Thymoquinone with improved kinetic and reduced toxicity. It deals with therapeutic effects and provides compendious review on nano-systems of Kalonji with the aim to develop novel pharmaceutical nanoformulation for critical illnesses.

Keywords: Kalonji; Thymoquinone; Nanotechnology; Nanoformulations; Bioavailability

INTRODUCTION

The name *Nigella sativa* is derived from the Latin word, *nigellus* which means black. It belongs to the family of Ranunculaceae plant [1]. In recent times, there is a significant growth in the use of the herbal drugs for the medicinal purposes compared to the chemically synthesized drugs because of the multiple advantages i.e. cheapest, fewer side effects with no need for the prescription of the herbal drug available in the market [2]. *Nigella sativa* is known with different names in different countries, for example, in Arab as Al-habbah, Al-Sawda or Habbet-el-Baraka; In America as Black cumin; in China as Hak Jung Chou; In Bangladesh as Kalijeera; while in Europe as Ajenue [3,4].

N. sativa seeds mainly contain thymoquinone, thymol, cymene, carvacrol, g-tocopherol, t-anethole, 4-terpineol, longifoline and all-trans retinol are confirmed in seed oil through GC-MS (Gas Chromatography Mass Spectrometry) [5-7]. Few of their structure mentioned as thymoquinone in (Figure 1a), thymol (Figure 1b) and thymohydroquinone (Figure 1c) were identified as pharmacologically active constituent of volatile oil. Nigellone (Figure 1d) [8,9]. Thymoquinone (TQ) was first isolated in 1963 from *Nigella sativa* essential oil. Afterwards, it was isolated from essential oil of *Eupatorium ayapana*[10] and *Calocedrus decurrens* [11] also from leaves of different *Origanum* species [12], oil of various *Satureja* species[13], *Nepetadistans* [14], and aerial flowering parts of *Thymus vulgaris* [15]. In combination therapy of TQ with chemotherapeutic agents showed enhanced efficacy compared to chemotherapy alone [16].

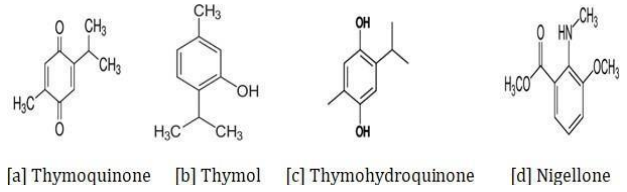


Figure 1: Chief chemical constituents of *Nigella sativa* seeds of (a) thymoquinone, (b) thymol, (c) thymohydroquinone and (d) nigellone.

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Nigella sativa seeds extract, essential oil and thymoquinone are reported for the treatment and prevention of various ailments such as diabetes [17], renal injuries [18], asthma [19], depression [20,21], headache, migraine [22], infertility [23,24], hyperlipidemia [25,26], neurological disorders [27], gastrointestinal diseases [4,28,29], liver diseases [30,31], and various types of cancers [32-35].

TQ has been reported to inhibit colon cancers and their invasion by inducing cell cycle arrest and apoptosis in both *in vitro* cell line and also in the animal model [36-39]. TQ has been shown to reduce toxicity related to chemotherapeutic agents [40-44]. TQ anticancer properties against breast cancer cell lines are reported due to its action on Peroxisome Proliferator-Activated Receptors (PPARs) [45] and nuclear/transcription factor (NF)-kB [46]. It also shows chemo preventive activities in cancer [47-51]. Dajani et al. provide an updated review on the pre-clinical pharmacological actions of *N sativa* in the fields of oncology, neurology, and rheumatology and in infectious diseases due to the presence of thymoquinone and other important bioactive components [48,52-57].

Nanoparticles (NPs) provide sustained, controlled delivery of the herbal drugs and protect from chemical and physical degradation [58]. It could improve the bioavailability and delivery of TQ as well as targeting and its extract and prevent from protein binding [59]. NPs may also increase the stability of the volatile components with improved patient compliance [60-63]. Herbal drugs can be incorporated, entrapped, attached or encapsulated into NPs [61]. It loaded with anticancer agents can successfully improve drug concentration in tissues and also act at cellular levels resulting in enhanced antitumor efficacy [64,65]. This review is an attempt to provide comprehensive analysis of the recent nanotechnological techniques and their application on Nigella extract and thymoquinone.

BIOPHARMACEUTICAL CHALLENGES IN DELIVERY OF *N. sativa* AND IT'S BIOACTIVE COMPONENTS

The main problem with the use of herbal products during the treatment is their low bioavailability [7,36]. Similarly, the applications of flavanoids as functional foods in natural remedy are limited because of their poor oral bioavailability [38].

The major drawback of TQ for its clinical applications is its poor pharmacokinetics i.e. the low volume of distribution (Vd), and high plasma protein binding [49]. Its hydrophobicity, light and pH sensitivity limit its bioavailability [50]. Currently, various types of nanoformulations have been developed to overcome limitations and obtain an effective delivery [52-57].

Nanoformulations of *Nigella*

Sahu et al. reported that NFs are efficient drug delivery systems for the targeted delivery of lipophilic antineoplastic agents as it possess certain advanced properties like biocompatibility, non-immunogenic, biodegradable, drug encapsulation efficiency, controlled release, ease of preparation and thermodynamic stability compared to traditional emulsions (Figure 2) [62].

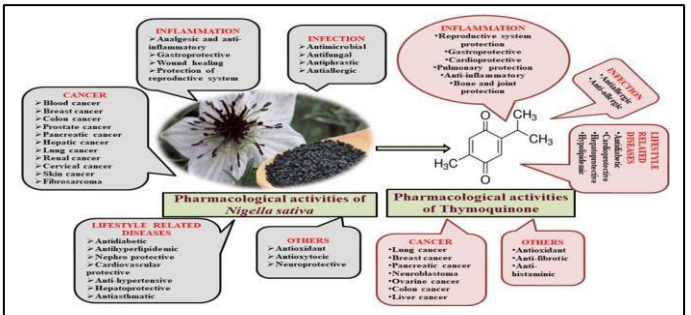


Figure 2: Pharmacological Properties of Nigella sativa and Thymoquinone.

N sativa Essential Oil Nanoemulsion (NSEO-NE) for breast cancer

Nigella EOs can be used as drug carriers and can provide a long shelf-life to anticancer agents, antimicrobials, larvicidal, insecticides and mosquito repellents [66-70]. Periasamy et al. developed NE of NSEO as described in Figure 3. NSEO-NE inhibited growth of breast cancer cells i.e IC_{50} value in the treatment group was 82±8.6 µl/ml in 24 hr, whereas 59±4.5 µl/ml in the 48 hours. The MCF-7 cells were treated with 40 µl/ml and 80 µl/ml of NSEO NE for 24 h, and showed 44% apoptosis and 28% necrosis. In conclusion it appears that NSEO nanoemulsions induced significant apoptosis in MCF-7 cancer cells [71].

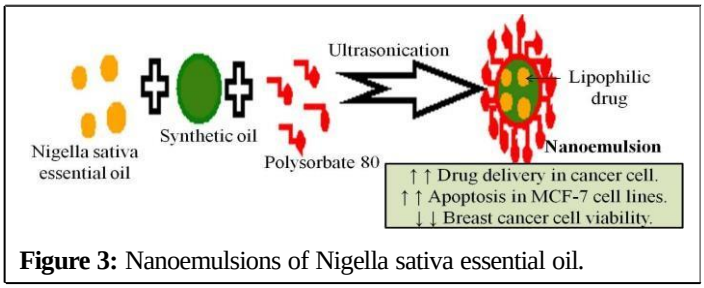


Figure 3: Nanoemulsions of Nigella sativa essential oil.

Nanogels of NSEO for antibacterial property

Jufri and Natalia, formulated NE gels using black seed oil and carried out its antibacterial testing. Furthermore, NEs gels revealed smaller inhibiting zone than pure kalonji oil ($P<0.01$) using PASW® Statistics 18 software [72].

NSEO SLNs for delivery of cosmetic and pharmaceuticals

Solid Lipid Nanoparticles (SLNs) have unique properties i.e. small size, great surface area, high drug loading capacity [73]. AL-Haj et al. reported SLNs of NS EO through high pressure hot homogenization technique. The re-crystallinity and polymorphic property of SLNs robustly affected drug entrapment and release behavior [74].

Thermosensitive co-polymeric micelles of *Nigella* extract for antibacterial

The thermosensitive polymers contain hydrophilic and hydrophobic groups that can create new structure and facilitate

release of active constituents of drugs in altered temperature [75]. Deepak et al. developed *Nigella* extract entrapped in thermo sensitive N-Isopropyl acryl amide-N-Vinyl 2-pyrrolidone (NIPAAm-VP) co-polymeric micelle by radical copolymerization method, outlined in Figure 4. Antibacterial activity of this formulation was evaluated against *B subtilis*, *S aureus* and *E coli*. Thermosensitive Co-Polymeric Micelles of extract was found to be 100 times more potent than pure Nigella extract. These micelles enabled temperature triggered release of extract within *in vitro* conditions. They could, therefore, produce an effective delivery *in vivo* in infectious states [76].

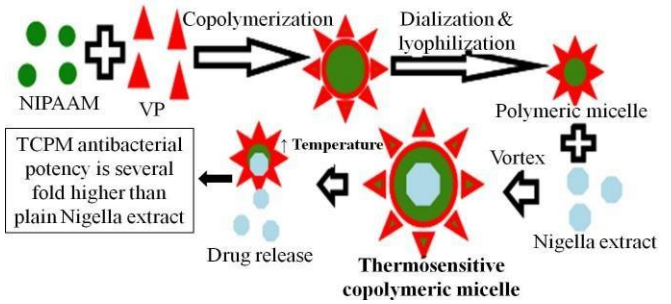


Figure 4: Nigella sativa extract entrapped in thermosensitive N-Isopropyl acryl amide-N-Vinyl 2-pyrrolidone (NIPAAM)co-polymeric micelle.

Metallic nanoformulations of extract

Gold Nanoparticles (GNPs) for antioxidant property: The optical properties of GNPs have been confirmed by the interaction of light with electrons on the surface [77,78] so, used in both bio-imaging and photonics. Fragoon et al. confirmed the antioxidant potential of phytoconstituents of Kalonji seeds, the potent phytoconstituents cause reduction of gold salt to its gold NPs. Nontoxic biocompatible NPs were developed as explained in Figure 5. As the amount of extract increased, the yield of nanoparticles will be increased [79].

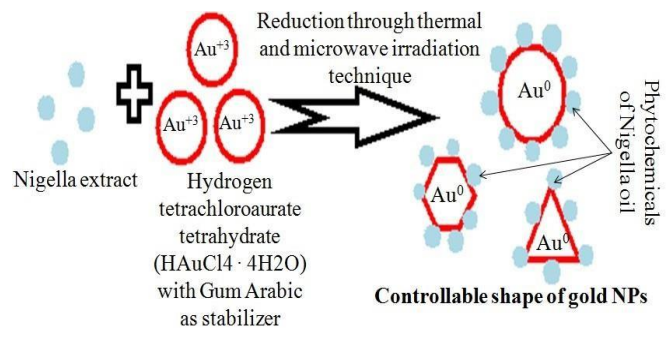


Figure 5: Gold nanoparticles of *Nigella sativa* extract.

Silver nanoformulations

Silver has antimicrobial properties so it was reported for improving the treatment of antibiotic resistance [80,81]. NFs have ability to inactivate bacterial enzyme by releasing ionic silver that inactivates thiol groups. Silver ion inhibits the bacterial DNA replication by depleting levels of Adenosine Triphosphate (ATP) and leads to cell death [82]. The first observation of silver NFs synthesis was observed in the color change of the formulation [83].

Silver nanoparticles against aquatic pathogens

Fragoon et al. developed silver Nanoparticles (NPs) of *N. sativa* seeds extract through one pot green synthesis. [79] The authors reported that the presence of the capping agent, obtained from Kalonji seed extract in nanoparticles may contribute to enhanced biocompatibility and additional therapeutic effects [84,85]. Further, Manju et al. synthesized silver nanoparticles of *N. sativa* EO to evaluate the inhibitory action against aquatic pathogens like *V. parahaemolyticus* and *V. harveyi*. The antibiotic film activity of Silver NPs of Nigella EO exhibits good inhibition of biofilm formation in case of *V. harveyi* followed by *V. parahaemolyticus* at 80 µg/ml. This process appears to be cost-effective alternative approach compared to conventional methods and would be suitable for developing a biological process for large-scale production [86].

Titanium dioxide doped silver nanoparticles (TiAgNPs) for anti-leishmanial property

TiO_2 doped silver NPs shows marked inhibitory effects on microorganisms compared with TiO_2 and silver NPs alone. Combination therapy usually provides an opportunity to reduce the toxicity of agents and enhanced their antimicrobial properties. *Abamor* and *Allahverdiyev*, reported that NSO incorporated TiAgNPs inhibited about 95% of cell growth in case of *L. tropicapromastigotes* parasitic disease. This report confirmed that the combination therapy reduced proliferation rates of *L. tropicapromastigotes* up to 15-25 folds, 2-4 folds metabolic activity, 5-20 folds the infection index values of macrophages. The effect was due to production of high amounts of nitric oxide and prevention of amastigote-promastigote conversion. The researchers confirm that TiAgNPs with NSO combinations were novel, safe and efficient treatment against Cutaneous *Leishmaniasis tropicapromastigotes* [87].

Silver nanorods for antidiabetic activity

Kumar et al. developed silver nanorods of N. sativa seeds and evaluated their antidiabetic activity against alloxan-induced diabetic mice model. Mentioned in Figure 6. The maximum absorbance observed at 446 nm confirmed the presence of silver nanorods [88]. The reduction of silver ions and stabilization of the silver nanorod was due to the participation of plant metabolites and coenzymes donate the electron for the reduction process [89,90]. Nanorods significantly decreased glucose level in alloxan-induced diabetic mice. Therefore, it could be used in the clinical practice for management of diabetes [88].

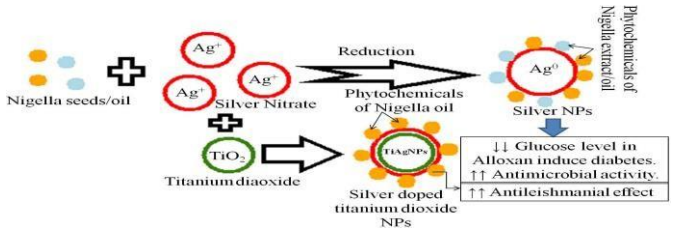


Figure 6: *Nigella sativa* oil incorporated titanium dioxide doped silver nanoparticles.

NANOFORMULATIONS OF TQ

TQ is a benzoquinone based phytoconstituents, exhibits various pharmacological activities [91-93]. Its poor water solubility leads to low absorption i.e 549 to 669 µg/ml at 24 h and 665–740 µg/ml at 72 h limit it's bioavailability [94]. Attempts have been made to synthesize novel NFs of TQ with improved bioavailability as described below and in Table 1.

Table 1: Various nanoformulations of Kalonji and TQ with significant findings.

Types of Nanoformulations	Active Component	Size in nm	*In vitro*/*In vivo* screening	Outcomes	References
Solid Lipid Nanoparticles (SLNPs)	*Nigella sativa* Essential Oil	66-143	-	Could be suitable as carriers in cosmetic and pharmaceutical fields.	[74]
	Thymoquinone	166.1 ± 10.96	Hepatoprotective	Bioavailability has increased up to ~5 fold in compared to TQ suspension further significant reduction of marker enzymes shown in compared to suspension of silymarin and TQ. Histopathological findings of liver showed treated animals restored the normal lobular architecture in compared to TQ suspension	[95]
		20-40	Neuroprotective	Bioavailability has increased up to ~5fold compared to TQ suspension. The drug distribution studies revealed TQ-SLNPs accumulated more in brain region than other organs due to its smaller size and high lipophilicity.	[98]
		172.1±7.41	*In vitro* Cytotoxicity	The electrical interaction force between Vero cell and particles were repulsive, so, decreased the interference of particle with the cell membrane and promoted cell viability through prevention of excess uptake of TQ-SLNPs.	[101]

		75 ± 2.5	Gastroprotective	Showed significant (97.6%) ulcer inhibition at 60 mg/kg dose. Immunohistochemical staining confirmed that TQ nanostructure lipid carrier has the ability to alter the expression of Hsp70.	[96]
Polymeric Nanoformulations	Thermosensitive Co-Polymeric Micelles of *Nigella sativa* Extract(TCPMNE)	75–110	Antibacterial activity	Showed significant antibacterial activity at 100 µg/ml dose, produced similar action as 2 mg/ml of pure *Nigella sativa* extract.	[76]
	TQ-encapsulated PLGA-NPs	<200	Antibacterial activity	Significant antibacterial activity compared to TQ suspension	[116]
	TQ loaded PLGA-chitosan nanoparticles	183.5 ± 8.2	Neuroprotective	Significant improvement in grip strength and locomotor scores in comparison to MCAO rats. Intranasal delivery of TQ-PLGA-CH-NPs showed better kinetics profile than oral route.	[99]
	TQ with topotecan and PLGA	<200	*In vitro* cytotoxicity	Cell viability was found to be >99%, so the NPs are free from any toxicity	[103]
	Paclitaxel–TQ PLGA NPs	227.53 ± 7.7	Anticancer effect on breast cancer cell line (MCF-7)	Paclitaxel-TQ loaded PLGA NPs produced synergistic anticancer activity in breast cancer cells (MCF-7).	[113]
	TQ-PLGA	100-200	Anticancer effect on breast cancer cell line (MDA-MB-231)	Nontoxic to normal cells whereas shown significant antiproliferative effect against MDA-MB-231 cells.	[104]
	TQ-PHA-mPEG	112–162	*In vitro* cytotoxicity	On cytotoxicity using prenatal rat neuronal hippocampal and fibroblast cells revealed that biocompatibility of the amphiphilic nanoparticles was generally independent of the ratio of co-monomer units in the polyhydroxyalkanoates (PHA) block.	[118]

	TQ with β cyclodextrin (TQ-CD)	445±100	Antiproliferative activity by MTT Assay	IC50 of 4.70±0.60 micro M for TQ-CD nanoparticles in comparison to 24.09±2.35 micro M of free TQ solution after 72 h of incubation. TQ loaded cyclodextrin nanoparticles might serve as a potential nanocarrier to improve TQ solubility as well as its antiproliferative activity.	[126]
	PEG4000-TQ	<50	Anticancer effect on breast cancer cell line (MCF-7 and HBL-100)	TQ-NPs showed more efficiency in killing cancer cells and showed the least toxicity to normal cells at a much lower dose compared to TQ. TQ-NPs showed potent antimigratory properties compared to TQ alone.	[114,119]
Metallic Nanoformulations (Silver Nanoparticles)	Silver Nanoparticles of *Nigella sativa* seed extract	3.8-14.6	-	Maybe screened for Antimicrobial activity, used in other medical applications due to the presence of thymoquinone as capping agents.	[84]
	Silver nanoparticles of NSEO	~96	Antimicrobial activity	Showed good inhibition of biofilm formation of *Vibrio harveyi* and *Vibrio*para haemolyticusat 80 µg/ml and 100 µg/ml.	[86]
	Silver doped titanium dioxide nanoparticles of *Nigella sativa* oil (TiAgNPs)	~90	Antileishmanial effect	N Sativaoil incorporated TiAgNPswas estimated for effect on cellular membranes through mitochondrial-mediated apoptosis. Results confirmed that disruption of cell membranes of Leishmania parasites were enhanced by NSO-TiAgNPs due to enhanced accumulation within the parasites and they may together attack concurrently to vital structures like DNA,	[87]

				enzymes and important proteins. It also enhanced the nitric oxide production of macrophages 4 to 9 times in compared to TiAgNPs alone.	
	Silver nanorods of *N. sativa* seeds	~77.7 nm	Antidiabetic activity in Alloxaninduced mice.	Significantly decreased glucose level from 300 mg/dl to 100 mg/dl on 14th day of nanorod administration in diabetic mice.	[88]
Gold Nanoparticles	*Nigella sativa*seeds Extract	5-30	-	Gold nanocrystals are highly anisotropic in nature, mainly hexagonal and triangular shapes. It would be practical value to utilize the anti-cancer effects of the main active phytochemical compound.	[79]
	Gold niosomes containing TQ and Akt-siRNA (siRNA-Nio-Au-TQ)	150	*In vitro* against tamoxifen-resistant (MCF-7/Tam and T-47D/TAM) and Akt-overexpressing (MCF-7/Akt)cell lines	In both cancer cell lines, treatment with siRNA-Nio-Au-TQ showed enhanced effects when compared with either free TQ or Nio-Au-TQ.	[120]
			In vivo in a BALBmouse xenograft model of MCF-7 cell	*In vivo* results indicated that decrease in tumor volume, when given intravenously for a period of 14 days to xenografted mice. It shows targeted delivery of TQ and Tmax was achieved in 120-180 mins.	
Nanoemulsion	Thymoquinone	~94.6	Neuroprotective	TQ-NE (intranasal) was showed significant improvement in neuromotor activity. Significantly increased the bioavailability and brain targeting efficiency of TQ compared to TQ solution.	[97]
		122	*In vitro* antiproliferative action using breast cancer cell	The results showed significant cytotoxicity	[121]

	lines MCF-7 and T47D	in MCF7 and T47D breast cancer cells whereas negligible effect in case of normal periodontal ligament fibroblast. It showed improved bioavailability as well as stability.	
100	Anticancer activity on breast cancer cell lines (MCF-7 and MDA-MB-231)	*In vitro*, TQ-NE had significantly equal anticancer activity effects compared to TQ in MCF-7 and aggressive MDA-MB-231 breast cancer cells.	[122]
92.17 ± 0.59	Memory test, Antioxidant, Gene Expression levels in brain cortex and hippocampus in high fat-cholesterol diet (HFCD) treated rats.	TQ-NE improved the behavioral changes, lipid peroxidation and soluble Amygloid beta levels compared to TQ suspension.	[123]

THYMOQUINONE NANOFORMULATIONS (TQ NFS) AS HEPATOPROTECTIVE

Solid Lipid Nanoparticles (SLNPs)

Singh et al. developed SLNs of TQ through a solvent injection method as summarized in Figure 7. The pharmacokinetic study of SLNPs revealed significant increase in absorption rate constant (Ka=2.364±0.109 h^{-1}) when compared to marketed formulation of TQSILYBON® [Ka = 1.54 ± 0.046, 5-fold increased bioavailability (AUC0→∞ = 2998.91±260.503 µg/ml h) than TQ suspension (484.23± 21.755 µg/ml h) [95].

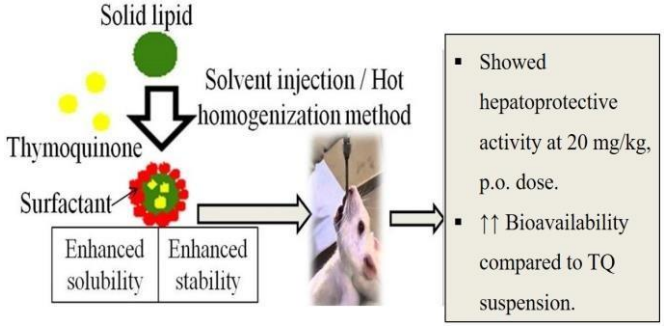


Figure 7: Thymoquinone loaded Solid lipid nanoparticles.

Hepatoprotective activity of SLNPs of TQ was evaluated in paracetamol (650 mg/kg/on the 7th day, p.o.) induced hepatotoxicity in Sprague Dawley (SD) rats at dose TQSLNPs (20 mg/kg/day, p.o.) and silymarin (40 mg/kg/day, p.o.) and TQ suspension (20 mg/kg/day, p.o.). Significant reduction in the increased level of serum enzymes in case of SLNPs were observed in compared to silymarin and TQ suspension. The researchers also reported that SLNPs can efficiently target HSCs in rats. Facilitated and passive targeting of SLNPs of TQ to the liver is more effective in compared to TQSILYBON®. Thus, it is a valuable approach for the treatment of liver fibrosis/cirrhosis. To take a step further, a prospective treatment to liver cirrhosis in the future could be achieved by suitably bonding mannose or galactose residues to nanocarriers for their specific and active uptake by hepatocytes [95].

Nanostructured Lipid Carrier (NLC)

Abdelwahab et al. evaluated the acute hepatotoxicity of TQ-NLC in rats and on normal human liver cells (WRL-68). The obtained IC50 of TQ-NLC (20.1 ± 0.9 µg/ml) was significantly higher than non-loaded NLC (10.5 ± 0.37 µg/ml), and the TQ-NLC treated rats showed considerable decrease in liver biomarkers levels compared to non-loaded NLC. The Linear pharmacokinetic parameters were observed in rabbit model [96].

THYMOQUINONE NANOFORMULATIONS (TQNFs) AS NEUROPROTECTIVE

Thymoquinone administration through intranasal route can be a useful process to bypass first pass metabolism and to achieve high drug concentrations to the cortex, hippocampus,

and caudate-putamen in comparison to intravenous administration. Intranasal route allows raised brain drug delivery as well as enhanced drug bioavailability, so low dose and improved pharmacological effects was observed compared to conventional formulations [97].

Solid Lipid Nanoparticles (SLNPs)

Surekha and Sumathi, formulated TQ loaded SLNPs targeted to the brain. After oral administration, the bioavailability of TQ-SLNPs was increased up to 5 folds than TQ-suspension. Further the drug distribution graph revealed more accumulation of TQ-SLNPs in the brain ($AUC0_{\rightarrow\infty}$ 66.921 ± 2.505 μg/g/h) rather than other organs. SLNPs may, therefore, be appropriate for brain-targeted drug delivery and suitable to treat age-related brain disorders [98].

Polymeric Nanoparticles (NPs)

PLGA is a suitable polymer for drug used in treating psychological and neurological disorders. Xiao et al. developed PLGA Chitosan Nanoparticles (TQ-PLGA-CH-NPs) by modified double emulsion solvent evaporation technique and evaluated for neuroprotective activity against cerebral ischemic reperfusion rat model. The intranasal pretreatment of TQ-PLGA-CH-NPs showed better protective effect and improved locomotor and muscle relaxant activity compared to the Middle Cerebral Artery Occluded (MCAO) rat model than the conventional oral delivery systems. The pharmacokinetic inference concludes the amount of TQ that reached the brain by the intranasal route was more than any other route. Further the biochemical parameters revealed that intranasal route significantly reduced the level of lipid peroxide enzyme, with enhanced production of glutathione, superoxide dismutase and catalase enzymes in the middle cerebral artery occluded rats. The results indicated that intranasal administration of TQ-PLGA-CH-NPs may be a future alternative treatment approach for cerebral ischemia [99].

Thymoquinone Mucoadhesive Nanoemulsion (TMNE)

Ahmad et al. developed TQ loaded NE for intranasal delivery in MCAO induced cerebral ischemic Wistar rats. The Drect Transport Percentage (DTP %) of TQNE intranasal (i.n.) delivery as compared to TQ suspension showed significant increases from 33.23 ± 1.03 to 85.04 ± 7.29%. The pharmacokinetic findings indicate enhanced distribution of TQ to the brain and improved neurobehavioral activity by i.n route than i.v administration. Further it was found that encapsulation of drug protects from chemical and biological degradation and extracellular efflux by P-gp proteins, which further improve bioavailability of drug to CNS [100].

THYMOQUINONE NANOFORMULATIONS (TQNFS) FOR STOMACH ULCER

Abdelwahab et al. formulated TQ-NLCs. These were evaluated against ethanol induced stomach ulcer in SD male rats. Pretreatment with TQ-NLCs at a dose of 60 mg/kg showed significant (97.6%) ulcer inhibition compared with non-loaded lipid nanostructure. Additionally the immune histochemical staining confirmed that formulated NLC has ability to alter the expression of Hsp70 (heat shock proteins 70 kilodalton) [96].

THYMOQUINONE NANOFORMULATIONS AS ANTICANCER

TQ loaded Solid Lipid Nanoparticle (SLNPs)

Surekha et al. developed TQ loaded SLNPs by hot homogenization microemulsion technique. The cytotoxicity of TQ-SLNPs was carried out using Vero cell line (Derived from the kidney of an African green monkey). SLNPs showed reduced cytotoxicity compared with TQ suspension because SLNPs carried negative surface charge (-45.4±2.68 mV), for which, the electrical interaction between Vero cells and NPs were repulsive thus preventing excess uptake of it [101].

Nanostructured Lipid Carrier (NLCs)

Ng et al. prepared TQ-NLC through hot high-pressure homogenization technique. It showed antiproliferative and cytotoxic activity towards breast cancer cell lines MDA-MB-231 than MCF-7 and cervical cancer cell line SiHa. TQ-NLC was less cytotoxic towards 3T3-L1 and Vero cell lines. The ability of NFs to induce cytotoxicity through apoptosis in MDA-MB-231cells suggested that thymoquinone loaded NLCs could be a potentially effective therapeutic agent against breast cancer [102].

Polymeric nanoparticles

Polymeric nanoparticles of TQ are comparatively nontoxic, nonimmunogenic, lack thrombogenicity and have good stability profile [59]. Verma et al. developed TQ-Topotecan loaded PLGA NPs by the modified double emulsion solvent evaporation method. The MTT assay of blank NPs were carried out against human embryonic kidney cells 293 (HEK293) for 72 hours and did not show significant toxicity. The cell viability was found to be >99%. PLGA Loaded TQ nanoparticles were more effective than free TQ in inhibiting the growth of MDA-MB-231 breast epithelial cancer cells [103,104]. The TQ was reported to induce apoptosis in cancerous cells by modulating p53, p-Akt, NF-jB, PTEN, STAT3, p21, Bcl-2, caspases,molecular targets, and inhibiting tumor angiogenesis [105-108].The combinational drug delivery resulting synergistic effect by enhanced target selectivity, reduced drug resistance, and minimizes side effects [109-112].

Soni et al. prepared TQ and paclitaxel-loaded NCs using the solvent-evaporation technique and were evaluated for anticancer potency using MCF-7 cell line. Combinational NPs were more effective than paclitaxel NPs alone. Accordingly, TQ entrapment reduced the effective concentration of paclitaxel. The outcome showed that paclitaxel+TQ loaded PLGA NPs produced

synergistic anticancer activity in breast cancer cells (MCF-7) at low dose [113].

Bhattacharya et al. synthesized TQ NPs using hydrophilic polymers like PVP and PEG to increase TQ solubility. PEG-TQNPs prepared by the nanoprecipitation method exhibited strong specificity to breast cancer cells through up regulation of miR-34a in a p53-dependent manner at a significantly lower dose than TQ [114]. The PF127-TQ showed IC 50 of 20, 8 and 7 μM after 24, 48 and 72 h respectively while PF68-TQ showed IC 50 30, 18, and 12 μM, within the same time. The PF127-TQ, therefore, appeared to be more potent than PF68-TQ and produced higher toxicity to MCF-7 cells compared to PF68-TQ [115].

TQ loaded PLGA NPs as Antimicrobial and Antioxidant

Nallamuthu et al. formulated TQ loaded PLGA NPs by solvent evaporation method using PVA as a stabilizer. The TQ-PLGA NPs showed 71.23 % DPPH radical scavenging capacity at concentration 1000 μg/ml. NPs showed significant antibacterial activity against *E. coli*, *S typhi* and *S aureus* by providing zone inhibition diameter of 6 and 7 mm by agar diffusion method [116].

DISCUSSION

In this review we have discussed the evaluation of Kalonji extract and TQ in NFs for their antitumor, antidiabetic, hepatoprotective, gastroprotective, neuroprotective, and antibacterial effects. There are different routes for administration of TQ including intravenous (i.v), intraperitoneal (i.p.) and oral subacute and sub-chronic administration [117-128]. However, oral administration could lead to biotransformation due to the metabolizing activity of the liver enzymes [122]. Recently, Kalam et al. reported that Self-Nano Emulsifying Drug Delivery Systems (SNEDDS) of TQ (10 mg/kg, p.o) showed enhance oral bioavailability by 3.87 fold and improved hepatoprotective activity compared to TQ suspension (10 mg/kg, p.o) and silymarin (20 mg/kg, p.o) in Wistar rat with Carbon Tetrachloride (CCl4) induced hepatotoxicity [129].

The nanoformulations included SLNs, polymeric micelles, NLCs, metallic NPs and nanoemulsions [116]. According to Ballout et al. despite the promising anticancer activities of TQ, its translation to the clinic is still limited. Cascella et al. studied N. sativa/ TQ and concluded that it could have a significant role in preventing and retarding the progression of Alzheimer's disease and possessed good *in vitro*/*in vivo* findings [93]. Recently, Rani et al. have reported that nanocapsule of TQ produced better antihyperglycemic effect at dose 20 mg/kg, p.o, compared to TQ alone [130].

In another research, Nahla et al. observed that co-delivery of Doxorubicin with TQ in gel nanofibers showed improved anticancer effect against MCF-7 and Hep G2 cell lines According to them, this co-delivery leads to decreased nephrotoxicity of doxorubicin and increase of the chemotherapeutic effect. NFs can not only sustain/control drugdelivery but also protect the bioactive or extract from physicochemical degradation [131].

CONCLUSION

This review comprises the findings of various researchers which can be utilized to design a novel targeted delivery system for some serious physiological co-morbid conditions still difficult to handle with conventional therapeutic approaches. In conclusion, we assume that the research along with natural products/ phytochemicals and these novel delivery carriers will develop attractive treatments, which may provide a better therapeutic approach rather than the conventional therapy in the times to come.

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CONFLICTS OF INTEREST

The authors have no conflict of interest, financial or otherwise.

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