RESVERATROL NANOPARTICLE’S FORMULATION - IN DIABETIC NEPHROPATHY

Dr. Navneet Omprakash Soni*

Centre for Research in Molecular Pharmacology Plot no 3, Shramik Coloney, Laxminagar, Sangli 416146 Maharashtra, India.

ABSTRACT
Resveratol a powerful antioxidant but having poor solubility, poor bioavailability, short half-life and chemically unstable. Such compound is changed and transformed to novel drug by using nanoparticles/nano-formulation which not only overwhelmed the problems of free Resveratrol but also provided site specific delivery and unique accumulation of particles inside the cell especially mitochondria which may be helpful to prevent ROS mediated injury particularly in Diabetic nephropathy.

KEYWORDS: Resveratrol, Nanoparticles (NPs), Diabetic Nephropathy (DN).

INTRODUCTION
Chemically: Resveratrol is polyphenol and phytoalexin occurring in nature. (Chemically it is -3,5,4’-trihydroxystilbene) (Guo et al., 2013).


Commonly consumed in diet: Resveratrol is commonly consumed in the human diet from sources such as red wine, grapes and peanuts (Karthikeyan et al., 2013).

Isomers: Resveratrol occurs in two geometric isomers, cis- and trans (Montsko et al., 2008). The trans-isomer is plentiful and biologically active as compared with the cis-isomer (Augustin et al., 2013; Rius et al., 2010).
ADME OF RESVERATROL

Absorption
trans-epithelial diffusion.

Bioavailability
Bioavailability less than 1% (Walle, T., 2011).

Low bioavailability is due to
Extensive metabolism mainly in the intestine and liver. (Walle, T., 2011).

Metabolism and metabolite metabolism
Glucuronic acid conjugation and sulfation to produce the main metabolites, named as trans-resveratrol-3-O-glucuronide and transresveratrol-3-sulfate. Only trace amount of free drug is found in the systemic circulation. (Walle, T., 2011).

Pharmacological property
Cardioprotective, Anti-inflammatory, Antioxidant and Anticancer properties, also used in DN (Aluyen et al., 2012; Kraft et al., 2009; Jang et al. 1997; Soni NOP 2017; Yang et al., 2014).

Advantages of Nanoparticles (NPs)
1) NPs tend to extravasate passively through the leaky vasculature. (Sanna, Vanna, et al. 2012).
2) Favourably accumulate through the enhanced permeability and retention (EPR) effect (Sanna, Vanna, et al. 2012).
3) Increased drug concentration close to the cell membrane generates a concentration gradient that helps drug influx into the cell. (Sanna, Vanna, et al. 2012).
4) NPs are taken up by cells through an endocytosis pathway and higher cellular uptake of the entrapped drug, thereby allowing them to escape from the effect of P-glycoprotein pumps. (Sanna, Vanna, et al. 2012).
5) Reducing drug particle size is an effective and commonly adopted approach to increase solubility and speed up dissolution by amplifying the effective surface area. Particularly when particle size is reduced to the nanometric state, the dissolution rate is proportional to the surface area available for dissolution as well-defined by the Noyes-Whitney equation. (Hao, Jifu, et al. 2015).
6) The absolute solubility of nanosized active component is also obviously altered in the light of Ostwald-Freundlich equation. (Hao, Jifu, et al. 2015).
7) Natural polyphenols- In NPs form improves their pharmacokinetic properties and bioavailability. (Sanna, Vanna, et al 2012).

Why nano formulation of Resveratrol
The need of nano-formulation is due to pharmacokinetic properties (Neves, Ana Rute, et al. 2013), since the compound has
1) Poor bioavailability,
2) Low water solubility, and,
3) Chemically unstable.
4) Short biological life.

Preparation method and formulation of nanoparticles of Resveratrol
1) Kim, Sanggu, et al 2012- Improve the oral bioavailability, trans-resveratrol (t-RVT) nanoparticles were primed by temperature-controlled anti-solvent precipitation with the hydroxypropyl methylcellulose as the stabilizer.
2) Sanna, Vanna, et al 2012- Resveratrol-loaded Nano Particles were prepared by a nanoprecipitation method.
3) Neves, Ana Rute, et al. 2013- solid lipid nanoparticles (SLNPs) and nanostructured lipid carriers (NLCs) loaded with resveratrol were fruitfully produced by a modified hot homogenization technique.
5) Hao, Jifu, et al. 2015: Resveratrol nanosuspensions prepared by liquid anti-solvent precipitation technique.
6) Park, Sun Young, et al 2016: Green synthesis and characterization of Resveratrol –gold NPs (RESVERATROL–Au NPs): RESVERATROL-AuNPs were prepared by the reduction method using chloroauric acid.
7) Summerlin, Natalie, et al 2016: MCM-48 synthesis was performed with slight modifications to the method reported by Kim et al 2012.

Advantages of solid lipid nanoparticles (SLNPs)
3) Lipid nanoparticles are submicron colloidal carriers composed of biodegradable and biocompatible lipids that are usually recognized as safe and appropriate for the incorporation of lipophilic and poorly water soluble active ingredients such as resveratrol, helping its oral absorption. (Neves, Ana Rute, et al. 2013).

4) In fact, lipid nanoparticles have a superior capacity to penetrate cell membranes, permitting the increased cellular uptake of compounds when they are loaded with. (Neves, Ana Rute, et al. 2013).

5) Nanodelivery systems is appropriate carriers for oral administration, conferring protection to the incorporated resveratrol and allowing a controlled release after uptake. (Neves, Ana Rute, et al. 2013).

Thus physical and chemical protection conferred to resveratrol by these lipid nanoparticles will enhance the therapeutic effects of resveratrol by minimizing its instability in vivo and controlling its release profile. (Neves, Ana Rute, et al. 2013).


1. Polymeric materials, poly (d,l-lactide-co-glycolide) (PLGA) is a extensively used copolymer permitted by the FDA for various medical and pharmaceutical applications, such as drug delivery. (Sanna, Vanna, et al 2012).

2. The blend of PLGA as a hydrophobic polymer and many natural hydrophilic biopolymers like gelatin or sodium alginate (Alg) provides benefits both the hydrophilic and the hydrophobic nanoparticulate systems. (Sanna, Vanna, et al 2012).

3. Chitosan (CS) and Alg are two main naturally occurring polysaccharides with hydrophilic characteristics that have growing interest in the biomedical field, and predominantly in the drug-delivery zone. (Sanna, Vanna, et al 2012).

4. NPs produced are spherical in shape, with size ranging from 135 to about 580nm. (Sanna, Vanna, et al 2012).


6. This type of Nanosystems are capable to prevent the degradation of trans isoform and the leakage of resveratrol from the carrier for a period of six months. Furthermore greater surface area and the potential to increase solubility, stability, bioavailability, and
controlled release as well as targeted delivery of the encapsulated active agents. (Sanna, Vanna, et al. 2012).


10. Production yield is also good with this method. (Sanna, Vanna, et al. 2012).

Resveratrol (RESVERATROL)-loaded polysorbate 80 (PS80)-coated poly(lactide) nanoparticles
RESVERATROL-loaded nanoparticles (but not bulk) displayed significant neuroprotection against MPTP-induced behavioral and neurochemical change. (Gabriela da Rocha Lindner et al 2015).

DRAWBACK OF POLYMER NPs
Particle-particle aggregation makes physical handling of nanoparticles difficult in liquid and dry form. (Jawahar, Natarajan, and S. N. Meyyanathan. 2012).

RESVERATROL NANOSUSPENSIONS-ADVANTAGES
1) Increase in saturation solubility and very fast dissolution rate (Hao, Jifu, et al. 2015).

2) Nano-suspension - raises the probability of obtaining higher therapeutic concentration generating desired pharmacological action and makes them superior to other colloidal drug delivery systems. (Hao, Jifu, et al. 2015).

3) The nanosuspensions provide a larger surface area for dissolution and molecular dispersion of resveratrol obtained from solubilized nanoparticles. (Hao, Jifu, et al. 2015).

4) Increase in adhesion surface area between nanoparticles and intestinal epithelium of villi involving a direct contact with the absorbing membranes of the gut and immediate release of drug accessible at the site of absorption might be additional reason for the improved absorption of the nanosized drug particles. (Hao, Jifu, et al. 2015).

5) Nano suspension drug formulation - drug may escape from the liver metabolism also increasing bioavailability. (Hao, Jifu, et al. 2015).
Resveratrol loaded Gelatin nanoparticles (RESVERATROL-GNPs)

Using RESVERATROL-Gelatin Nanoparticles Advantages

1) Gelatin is a naturally occurring protein based biopolymer with comparatively low antigenicity. It has been used for years in parenteral formulations and accepted as plasma expander. Its biodegradability, biocompatibility, chemical modification potential and cross-linking probability make gelatin-based nanoparticles a capable carrier system for drug delivery. (Karthikeyan, S., et al 2013).

2) Several investigations showed glutaraldehyde as an effective cross-linker that gives stability, shape and an enhanced circulation time to GNPs. The aldehyde groups of glutaraldehyde and the amino groups of gelatin undertake Schiff base reaction and form a network assembly, which will support stabilization and controlled release of RESVERATROL-GNPs (Karthikeyan, S., et al 2013).

3) RESVERATROL-GNPs demonstrated very rapid and more efficient cellular uptake than free RESVERATROL. (Karthikeyan, S., et al 2013).

4) RESVERATROL-GNPs treatment showed superior antiproliferative efficacy than free RESVERATROL (Karthikeyan, S., et al 2013).

5) Further treatment in NCI-H460 cells lines greater ROS generation, DNA damage and apoptotic occurrence in RESVERATROL-GNPs treated cells than free RESVERATROL treatment. (Karthikeyan, S., et al 2013).

6) Erythrocyte aggregation assay displayed that the prepared RESVERATROL-GNPs formulation elicit no toxic response. (Karthikeyan, S., et al 2013)

7) HPLC analysis exposed that RESVERATROL-GNPs was more bioavailable and had a longer half-life than free RESVERATROL. (Karthikeyan, S., et al 2013).

8) Henceforth, GNPs carrier system might be encouraging approach for controlled delivery and for enhanced therapeutic index of poorly water soluble RESVERATROL. (Karthikeyan, S., et al 2013).

Gold-conjugated resveratrol nanoparticles (Park, Sun Young, et al. 2016)

1) AuNPs have been developed as an significant tool for medical applications. The biological synthesis of AuNPs is eco-friendly and perfect method to develop environmentally workable nanoparticles (Park, Sun Young, et al. 2016).

2) In the breast cancer cells, and in the existence of RESVERATROL-AuNPs, the TPA-induced migration and invasion activity diminished. The extracellular matrix regulates numerous cellular functions necessary for tumour invasion and extracellular matrix
components (i.e., MMPs) are main mediators of this progression. Activation of MMP-9 is linked with increased cell invasion, angiogenesis, as well as aggressive breast cancer. A specific inhibitor of MMP-9 is TIMP-1 and MMP-2 is regulated by TIMP-2. (Park, Sun Young, et al. 2016).


4) It also inhibits signalling molecules tangled in cancer invasion, such as MMP-9, COX-2, NF-κB and AP-1. (Park, Sun Young, et al. 2016).

**Colloidal mesoporous silica nanoparticles enhance the biological activity of resveratrol**

1) Resveratrol’s poor aqueous solubility, which limits its biological activity encapsulating resveratrol in colloidal mesoporous silica nanoparticles (MCM-48- RESVERATROL) increases its saturated solubility by ~95%. (Summerlin, Natalie, et al 2016).


3) MCM-48-RESVERATROL displayed high loading capacity (20% w/w) and outstanding encapsulation efficiency (100%). (Summerlin, Natalie, et al 2016).

4) While tested against HT-29 and LS147T colon cancer cell lines, MCM-48-RES-mediated in vitro cell death was higher than that of pure resveratrol, mediated via the PARP pathways. (Summerlin, Natalie, et al 2016).


6) Silica or silicon has numerous versatile and broad range of benefits such as non-toxicity, biocompatibility, biodegradability, high surface area, pore volume, homogenous distribution of guest molecules in porous space, the ability for surface charge control, and free dispersion throughout the body. (Fan J et al 2011).

7) Main drawback of porous silica nanoparticles is recognized to the surface density of silanol groups interacting with the surface of the phospholipids of the red blood cell membranes subsequent in hemolysis. Additional drawback is related to metabolic changes induced by porous silica nanoparticles leading to melanoma promotion. (Bharti, Charu, et al 2015).
Liposomes (Catania et al., 2013; Coimbra et al., 2011; Lu et al., 2012a; Narayanan et al., 2009; Wang et al., 2011).

Particle size: 100–120nm.

Solubility: 95% Increased resveratrol aqueous solubility.

Superior cytotoxicity in He-La and HepG2 cell lines in vitro.

Reduced growth of subcutaneous head and neck squamous cell carcinoma.

Drug loading: Very poor drug loading capacity <3%.

Stability: poor stability.

Enhanced cellular uptake and selective accumulation at the mitochondria on human lung cancer A549. Inhibited cell growth and induced apoptosis in vitro and in vivo.
<table>
<thead>
<tr>
<th>Formulation</th>
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<th>Drug loading</th>
<th>Efficiency &amp; cell uptake</th>
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<tr>
<td>solid lipid nanoparticles</td>
<td>100-200nm</td>
<td>poor</td>
<td>Increased cell uptake</td>
<td>Physical stability</td>
<td>Enhanced bioavailability Easy synthesis low cost</td>
<td>Poor drug loading</td>
<td>Neves et al 2013</td>
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<tr>
<td>Polymeric nanoparticles</td>
<td>100-360nm</td>
<td>moderate</td>
<td>Efficiency 95%</td>
<td>Good stability</td>
<td>Absorption is at constant rate Control release Decreased toxicity&amp; occurrence adverse drug reactions. Better drug utilisation Site-specific targeting can be achieved by attaching targeting ligands</td>
<td>Costly and tedious Synthesis Handling is difficult</td>
<td>Sanna, Vanna, et al 2012 Jawahar et al 2012</td>
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<tr>
<td>Colloidal mesoporous silica nanoparticles</td>
<td>50 and 100 nm. 20% W/W</td>
<td>Encapsulation Efficiency 100%</td>
<td>solubility increased 95%</td>
<td>Increased in vitro release kinetics. non-toxicity, biocompatibility biodegradability high surface area, pore volume, homogenous distribution of guest molecules in porous space, the ability for surface charge control, and free dispersion throughout the body.</td>
<td>Haemolysis Melanoma</td>
<td>Summerlin et al 2016 Bharti et al 2015 (Fan J et al 2011)</td>
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<td>Liposomes</td>
<td>100–120nm</td>
<td>poor drug loading</td>
<td>Increased Cellular uptake</td>
<td>95% Increased resveratrol aqueous solubility</td>
<td>Enhanced mitochondria accumulation poor stability poor drug loading</td>
<td>Costly to produce poor targeting in cancer therapy.</td>
<td>Catania et al., 2013; Coimbra et al., 2011; Lu et al., 2012a; Narayanan et al., 2009; Wang et al., 2011</td>
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<td>Cyclodextrins (CD)</td>
<td>5-10nm</td>
<td></td>
<td>Increase resveratrol aqueous solubility</td>
<td>Improve resveratrol cytotoxicity in HeLa, Hep3B and MCF-7 cell lines</td>
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<td>Ansari et al., 2011; Lu et al., 2012b; Silva et al., 2014; Venuti et al., 2014</td>
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ADVANTAGES OF RESVERATROL–NPs

I] RESVERATROL-NPs REDUCES OXIDATIVE STRESS
Yin, Haitao, et al. 2014 - Resveratrol-loaded nanoparticles decrease oxidative stress induced by radiation or amyloid-in transgenic caenorhabditis elegans.

II] ANTI –PROLIFERATIVE ACTION
Solid-lipid NPs loaded with Resveratrol decreases cell proliferation and demonstrated potential benefits for prevention of skin cancer. (Neves, Ana Rute, et al. 2013).

RESVERATROL-GNPs treatment displayed greater antiproliferative efficacy than free RESVERATROL (Karthikeyan, S., et al 2013).

III] INCREASED CYTOTOXICITY IN CANCER CELLS
Resveratrol –based NPs resulted in significantly higher cytotoxicity against malignant glioma cells. (Park, Sun Young, et al. 2016).

MCM-48 –RESVERATROL -While tested against HT-29 and LS147T colon cancer cell lines, MCM-48-RES-mediated in vitro cell death was higher than that of pure resveratrol, mediated via the PARP pathways. (Summerlin, Natalie, et al 2016).

IV] INHIBITION OF TRANSCRIPTION FACTORS AND ENZYMES
Inhibitory effect of RESVERATROL-AuNPs on MMP-9, COX-2, NF-κB, AP-1, PI3K/Ak and ERK activation (Park, Sun Young, et al. 2016).


V] INCREASED BIOAVAILABILITY AND HALF LIFE
Resveratrol-GNPs was more bioavailable and had a longer half-life than free Resveratrol (Karthikeyan, S., et al 2013).

Nano suspension drug formulation - drug may escape from the liver metabolism also increasing bioavailability. (Hao, Jifu, et al. 2015).

Increase in adhesion surface area between nanoparticles and intestinal epithelium of villi connecting a direct contact with the absorbing membranes of the gut and immediate release.
of drug accessible at the site of absorption might be additional reason for the improved absorption of the nanosized drug particles. (Hao, Jifu, et al. 2015).

VI] INCREASED CELLULAR UPTAKE
Resveratrol-GNPs demonstrated very rapid and more efficient cellular uptake than free Resveratrol. (Karthikeyan, S., et al 2013).

VII] HIGHER THERAPEUTIC CONCENTRATION
Nano-suspension -raises the probability of obtaining higher therapeutic concentration generating desired pharmacological action (Hao, Jifu, et al. 2015).

VIII] PROTECTS DEGRADATION OF RESVERATROL
Encapsulation provides substantial protection against light-exposure degradation, by decreasing the trans–cis photo-isomerization reaction. (Sanna, Vanna, et al. 2012). Nanosystems are capable to prevent the degradation of trans isoform and the leakage of resveratrol from the carrier for a period of six months. (Sanna, Vanna, et al 2012).

IX] FAVOURS SOLUBILITY, STABILITY, CONTROLLED RELEASE

Encapsulating resveratrol in colloidal mesoporous silica nanoparticles (MCM-48-RESVERATROL) improves its saturated solubility by ~95%. (Summerlin, Natalie, et al 2016).

X] SYNERGISM AND COMBINATION OF DRUGS IN RESVERATROL-NPs
In vivo, oral administration of the liposome-encapsulated curcumin-resveratrol exhibited an increase in resveratrol and curcumin levels in the serum and prostate tissue and synergistcally improves their bioavailability and enhances their antitumor effect against prostate cancer. (Narayanan NK 2012).

XI] DAMAGE INDUCED BY NANOPARTICLES (NPs) CAN BE REPAIRED BY RESVERATROL (RESVERATROL)
Chen, Guifang, et al. 2007- TiO 2 nanoparticles will produce ROS under ultraviolet radiation and adding resveratrol can repair damage since resveratrol is potent antioxidant.
Thus from the above points (I TO XI) it is clear that nanoformulation of resveratrol (RESVERATROL-NPs) – increase solubility, increase bioavailability, increases biological half-life, reduces oxidative stress, increases site specific delivery, increased cellular uptake, prevents degradation and leakage when encapsulated, also if any damage by nanoformulation occurs due to ROS production by NPs could be repaired by itself since it is loaded with resveratrol which is powerful antioxidant thus nanoparticles have several advantages as compared to free resveratrol.

Resveratrol is used in diabetic nephropathy (Soni NOP 2017) antioxidant, cardioprotective, anti-inflammatory and anticancer properties (Aluyen et al., 2012; Kraft et al., 2009; Jang et al. 1997; Yang et al., 2014).

**RESVERATROL PHARAMACOLOGICAL ACTIONS**

1) Resveratrol improves oxidative stress and protects against diabetic nephropathy through normalization of Mn-SOD dysfunction in AMPK/SIRT1-independent pathway (Kitada, Munehiro, et al 2011).


3) Resveratrol protects diabetic kidney by attenuating hyperglycaemia-mediated oxidative stress and renal inflammatory cytokines via Nrf2–Keap1 signalling (Palsamy, P., and S. Subramanian 2011).


6) Xu, Feng, et al.2014- Resveratrol prevention of diabetic nephropathy is associated with the suppression of renal inflammation and mesangial cell proliferation.


9) Xu, Ying, et al. 2012- Resveratrol protects against hyperglycemia-induced oxidative damage to mitochondria by activating SIRT1 in rat mesangial cells.

10) Ding, Da-Fa, et al. 2010- Resveratrol attenuates renal hypertrophy in early-stage diabetes by activating AMPK.

11) Yun, Jung-Mi, et al. 2012- Resveratrol up-regulates SIRT1 and inhibits cellular oxidative stress in the diabetic milieu.

12) Li, Bing, et al. 2012- Nrf2 is activated by Resveratrol.

**CLINICAL TRIAL:** PHASE I trial - Resveratrol's Effects in Diabetic Nephropathy.

COMBINATION OF RESVERATROL+LOSARTAN IS USED (check on clinical trials.gov on date 20/07/2017).

ClinicalTrials.gov Identifier: NCT02704494.

First received: March 4, 2016.

Last updated: October 7, 2016.

Last verified: October 2016.

**DISCUSSION AND CONCLUSION**

**RESVERATROL-GELATIN NPs AND RESVERATROL–AuNPs**

Cannot be used since gelatin NPs produced ROS in cell lines (Karthikeyan, S., et al 2013) since ROS production is more in diabetes and plays key role in pathogenesis of diabetic nephropathy (DN) and RESVERATROL-AuNPs – gold and gold salts are itself nephrotoxic and such formulation cannot be used in spite of several advantages. All metal oxide nanoparticles generate ROS in cells which can effectively inhibited by resveratrol. (Fahmy, Baher, and Stephania A. Cormier; 2009) So using metal particles with resveratrol is not good approach in treating DN such approach may be useful for treating malignancy/tumour where selectivity cytotoxicity is needed furthermore colloidal mesoporous silica NPs can case haemolysis by interacting with phospholipid membrane of RBCs and also promote melanoma production which limits its use in renal disease. (Bharti, Charu, et al 2015).
POLYMERIC
NPs have aggregation makes physical handling of nanoparticles difficult in liquid and dry form. (Jawahar, Natarajan, and S. N. Meyyanathan, 2012) if this difficult is overwhelmed it becomes a useful Nano carrier for drug delivery in DN.

Liposomes have poor stability and poor drug loading but have tendency to deposit in the mitochondria of the human cell (Catania et al., 2013; Coimbra et al., 2011; Lu et al., 2012a; Narayanan et al., 2009; Wang et al., 2011), liposomes loaded with resveratrol may be useful in treating DN since the major source of ROS generation is the mitochondrial and plays vital role in pathogenesis of diabetic nephropathy. Resveratrol is antioxidant such NPs loaded with resveratrol mitigate symptoms of DN if pharmaceutical drawbacks are overwhelmed.

Some cyclodextrins are nephrotoxic and NPs of cyclodextrins cannot be used in DN and the potential to modify the pharmacokinetics of drugs when rapid dissociation does not occur (Peters, 2012).

So biocompatible, biodegradable, with good physical stability and efficient encapsulation and good drug loading capacity and fast cellular uptake of nanoparticle such material should be used for preparing Resveratrol–NPs for treating DN.

RESVERATROL-NPs inhibit MMP9 in cancer, NF-κB in cell lines, act as antioxidants this property can be used to treat DN. A study is published that resveratrol has no effect on MMP-9, COX-1, COX-2, or NF-κB mRNA levels in diabetic rats. (Yar, A. S., S. Menevse, and E. Alp 2011) but no study or data is available on RESVERATROL-NPs effect on MMP9, COX1, COX-2 or NF-κB in diabetic nephropathy.

Currently resveratrol has now entered phase I trial in combination with losartan study and study with nanoformulation is yet long way to go in trial.

Using liposomes or solid lipid or chitosan and alginate or nanosuspension has its own advantages as discussed above also combination of resveratrol and curcumin in formulation has its own advantages in treating DN since curcumin targets many factors i.e multifactorial (Soni NOP 2017) and it’s well known resveratrol inhibit progress of DN such combination of drug in nano form would be more beneficial to treat as compared to free form and its well proved in study that resveratrol and curcumin both have synergism and improves bioavailability, single formulation of RESVERATROL-NPs or RESVERATROL-curcumin
NPs should lead to early Mitigation and reversal of DN may occur if challenges of safe nanoformulation are met and further in-vivo studies are carried using such novel formulation to treat DN in animal model, however till date no study data of such combination of RESVERATROL-Curcumin NPs or RESVERATROL-NPs in DN is available and based on study, data and reports available till date warrants further investigation with such novel NPs.

CONFLICT OF INTEREST
The Author declares there is no conflict of interest regarding publication of this paper.

ACKNOWLEDGEMENT AND CREDIT
I give credit and acknowledge all author, scientist and researcher listed in my reference work.

DECLARATION
The author has not conducted any trial on human and animals and if the present paper includes any study it is taken from other reference source with appropriate citation done.

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