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Antioxidant activity and nano delivery of the most frequently applied stilbene derivatives: A brief and recent review

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ABSTRACT

As of recent, the appearance rate of several degenerative diseases and cancer influenced by oxidative stress continues to increase dramatically. Many compounds with high potential antioxidant activity have been explored and used extensively, i.e., as preventive or curative treatments. Stilbene and its derivatives have high potential antioxidant activity contained in several botanical sources. To date, source exploration and antioxidant activity study of stilbene derivate has been reported. However, the nano-delivery of stilbene derivate meant to increase the antioxidant activity and stability is still a limited process. This review is devoted to brief and recent outlooks regarding the antioxidant activity and delivery system of the most frequently applied stilbene and its derivatives, namely resveratrol and pterostilbene.

Keywords: resveratrol, antioxidants, nanoemulsion, nanoparticle, nano delivery

Introduction

Antioxidant activity is related to free radicals, which have unpaired electrons; hence, they can bind to other molecules to stabilise the radical structure. Free radical compounds can be formed from enzyme reactions in the body metabolism and exogenous sources, e.g., ultraviolet (UV) light or pollution. The human body has a mechanism that blocks free radical formation by neutralising them using several endogenous antioxidants and enzymes, e.g., catalase (CAT), super peroxide dismutase (SOD), glutathione peroxidase (GPX), thioredoxin and peroxiredoxin.[1] Excessive free radical compounds in the body can promote cell disruption, several chronic diseases or cancer. Therefore, our body requires an exogenous antioxidant to bolster the capability of endogenous antioxidants in stabilising excess free radicals.[2]

An antioxidant is a compound applied to prevent the free radical formation process through stabilisation and terminalisation of the free radical reaction itself.[3] Some antioxidant compounds, namely ascorbic acid and butylhydroxytoluene, sport a sufficiently high antioxidant capacity. However, they will immediately experience oxidisation and radicalisation due to higher potential oxidation value. In comparison, natural antioxidants such as bioflavonoid and phenolic compounds utilise different mechanisms to stabilise the radical molecules, particularly through an electron distribution mechanism at their chemical structure, i.e., resonance phenomenon. Therefore, this phenomenon can be applied to form stable antioxidant activity, which is a non-reactive compound. In addition, it can be implemented alternatively to prevent some diseases, i.e., chronic diseases or cancer mainly caused by oxidative stress.[2,4]

One of the most potentially powerful natural antioxidant compounds is polyphenol, a stilbene derivate found in various plant sources such as blueberry and bark fruit skin.[5,6] The most frequently applied stilbene derivate compounds, which comprise pterostilbene (PTS) and resveratrol (RSV), display strong antioxidant activity that protects biomolecules against oxidative stress, thus using antioxidants for preventive and curative therapy.[4] However, some limitations related to their solubilities and stabilities pose a noticeable challenge. The solubility problem regarding lipophilicity is a great consideration for drug development. Many drugs fail in the drug development and formulation process due to this problem. To provide better antioxidant capacity, the solubilised compounds serve primarily as a conduit for higher interaction with radical moiety. [7] Therefore, a soluble antioxidant, particularly in a biological medium, exists as a fundamental component of the drug development strategy. Significantly, not only could this antioxidant affect solubility, but stability could also reduce the antioxidant

capacity. Therefore, a physical barrier or protection is required to maintain the potency of antioxidants, particularly stilbene derivate, that undergo degradation due to photolabile compounds. [8,9]

Stilbene derivate can be directly formulated into conventional products, such as tablets, capsules, creams or ointment, without any modification. However, it will be ineffective due to the issues mentioned above. A nano-delivery-based formulation is the latest breakthrough among the current strategies designed to solve these problems as well as increase the antioxidant activity of stilbene derivatives. Several nano deliveries, e.g., polymeric nanoparticles, lipid-based formulation, nanocrystals, electro-spun nanofibres and cyclodextrin complexation, can increase solubility as well as its photostability. Subsequently, they can increase the bioavailability and potency of antioxidant activity .[10] Previous reviews regarding the RSV delivery have been reported but remains strictly limited to the selfsame system. [11] Hence, this short review discusses brief and recent outlooks regarding the exploration of the source of stilbene compounds, the antioxidant activity of stilbene derivate and their application in nano-delivery systems. Furthermore, the findings derived thereof can be put forth for further study or recommendations in the drug delivery and development process, particularly selecting a proper delivery system for the most frequently applied stilbene derivatives.

Article Selection Process

This short review was limited to original research articles published in 2015-2021 from Scopus, PubMed and Google Scholar databases. Some of the keywords applied include *stilbene derivate and source, resveratrol, pterostilbene, antioxidant activity of resveratrol, antioxidant activity of pterostilbene, resveratrol delivery, pterostilbene delivery, resveratrol antioxidant capacity, pterostilbene antioxidant capacity, resveratrol polymer based nanodelivery, resveratrol lipid based formulation, resveratrol nanocrystal, resveratrol cyclodextrin complexation, and resveratrol nanofibre electro spun*. Article selection and the results thereof took into account factors such as the critical appraisal parameters of the research objectives, methodology, illustration, results and discussion.

Article Database

There were 72 original research articles obtained according to the keywords and inclusion criteria. However, only 48 articles were selected according to the critical appraisal parameters. In addition, according to our findings, the number of articles significantly increased

year by year. Seemingly, this subject matter has progressively gained intrigue and therefore has excellent potential for further research contribution, particularly for developing a stilbene derivate delivery system.

Stilbene Derivatives and Their Sources

Stilbene is a polyphenol group compound with a C_6-C_2-C_6 building block and consists of two phenyl groups connected by ethene (Figure 1). The specific functional groups in the molecular structure are responsible for stabilising the antioxidant activity and resonance phenomenon. The hydroxy group plays a fundamental role in antioxidant activity that follows stabilisation through resonance in the double-bond conjugated alkyl chain.[12] Several stilbene derivate, i.e., RSV, PTS and 3-hydroxy-PTS, reportedly can be employed for anti-inflammatory, antioxidant, antidiabetic and dyslipidemia activities as well as cancer preventive treatment.[13] In addition, stilbene derivative compounds are found in several plants and plant parts, a list of which is presented in Table 1. There are four main compounds in stilbene derivate with therapeutic applications, namely RSV, PTS, trans-RSV and 3-hydroxy PTS, that stand out as the most frequently explored and abundant. RSV can be isolated from grapes, particularly in the skin, stem and seed.[14] Gharwalová et al. (2018) reported that, in grapes, the trans-RSV compound was also found.[15] Several marketed dietary supplements contain grape seed or its extract, which contains RSV. In addition, RSV was discovered in seeds and sprouts of Korean peanuts; seeds, skin and fruit in Jamun and jackfruit plants; and propolis extract.[5,16-17] With all sources in mind, RSV is most abundant in seed and skin of grapes.

PTS, one of the stilbene derivatives, exists plentifully in bark fruit skin and blueberries [18-21] as well as Indian kino plants.[7,22] Meanwhile, 3-hydroxy PTS, which is one of the PTS metabolites, can be isolated from all parts of the *Sphaerophysa salsula*, a type of shrub widespread in Central Asia and the Western China Sea.[13] These data in aggregate provide a clear and wide variety of stilbene sources. However, a new potential source of PTS has been explored that could be isolated from bark fruit skin.

Antioxidant Activity of Stilbene Derivatives

Trans-isomeric structure in RSV and PTS is dominantly responsible for the active form. In addition, the antioxidant activity of RSV and PTS depends on the elongation of hydroxylation and conjugation of double bond alkyl in their moiety. The antioxidant activity can be assessed and evaluated by the antioxidant capacity to measure amounts of radicals that

are blocked or scavenged by antioxidant compounds.[23] Direct measurement of antioxidant capacity is carried out by destroying chain radical's reaction, e.g., oxygen radical absorbance capacity (ORAC, β-carotene bleaching, and monoamine oxidase (MAO) enzyme kinetic assays. Indirect measurement of antioxidant capacity occurs through its ability to reduce stable coloured radicals, including the change in the colour of the solution, using spectrometric methods (e.g., 2,2-diphenyl-1-pycrylhidrazyl (DPPH), 2,2-azinobis-3-ethyl benzothiazoline-sulfonic acid [ABTS]) and ferric reducing antioxidant power (FRAP) methods.[24] Both direct and indirect methods can be applied for the evaluation of antioxidant activity, particularly for stilbene derivatives. The antioxidant activity measurement is divided into hydrogen atom transfer (HAT), single electron transfer (SET), and a combination thereof. ORAC and β-carotene bleaching test is included in HAT methods, while ABTS and FRAP methods involved in SET and DPPH categorise a combination of HAT and SET.[1]

Several of the most commonly used methods discovered in our review are summarised in Table 2. Namely, there are ORAC, DPPH, FRAP, ABTS, β-carotene bleaching test and MAO enzyme kinetic assay. ORAC assay enjoys the widest use because of its directness and simplicity. Amorati and Valgimigli (2015) reported that direct antioxidant capacity methods were more recommended than indirect due to how the autoxidation chain reaction broke.[24] Therefore, this eliminated the need for further oxidation reactions to be formed. In contrast, the indirect method is focused on the ability of antioxidants to inhibit the oxidation process. HAT-based test methods like ORAC and β-carotene bleaching test involve the inhibition of low-density lipoprotein peroxidation, and they are broadly used to measure the antioxidant capacity caused by the presence of radical species in biological media. However, HAT-based testing should also be strengthened with SET-based assays.[1] ORAC assay is simpler than another HAT-based assay due to the minimal requirement of reagent for reaction.

Duca et al. (2019) reported that the antioxidant activity of RSV, which was contained in propolis extract, was equivalent to that of ascorbic acid.[16] Several sources with antioxidant activity of RSV, ranging from highest to lowest, were grape seed, Jamun seed, mulberry fruit and jackfruit skin.[5] Previous work regarding the antioxidant activity of RSV was also reported by Luis et al. (2018). They mentioned that the antioxidant activity of RSV compounds was 19 times higher than that of vanillic acid, and it was equivalent to 0.3 times gallic acid [25].

Luis et al. (2018) also reported that the antioxidant activity of PTS was five times higher than that of vanillic acid, and it was equivalent to 0.1 times gallic acid through the DPPH method [25]. The antioxidant activity of PTS using the β-carotene bleaching test was 2.4 and 1.2

times higher than that of vanillic and gallic acid, respectively. RSV and PTS could inhibit monoamine oxidase enzymes that can promote oxidative stress, aging and several degenerative diseases. [26]

Our brief summary pointed out that the most potent stilbene derivate compound was RSV because their antioxidant capacity was the greatest in several methods, e.g., ORAC, FRAP and β-carotene bleaching assays. However, in the DPPH assay, the antioxidant capacity of PTS was higher than RSV; that is, the potential antioxidant activity of PTS was nine times greater than RSV. [22,16] ABTS assay was showed that the antioxidant capacity of oxy-RSV compounds was higher than PTS, RSV and pynosilvyn compounds.[6]

Nanodelivery of Stilbene Derivate

Studies of nanodelivery in pharmaceutics and biomedical purposes have increased dramatically in this decade. The purpose behind these efforts considers greatly enhancing activity or potency and breaking the boundary limits of poorly water-soluble compounds, e.g., solubility, permeability and stability.[27-29] Per the aforementioned discussion, stilbene derivate show great effectiveness in antioxidant activity, but low solubility and photostability limit their potency. Therefore, in order to address particular issues, i.e., reduction of antioxidant potency due to photostability, limited permeability and solubility, nano delivery can be applied. Encapsulation using lipid or polymer in nano-sized particles can enhance the stability correlated to the photostability, enzyme or pH as well as altering transport mechanisms. Reducing its size to less than 100 nm promotes tremendous improvement of fundamental characteristics, e.g., solubility and entrapment efficiency.[30] This review devotes special attention to the application of nano delivery to stilbene derivate, e.g., polymeric nanoparticles, lipid-based formulation, nanocrystals, electro-spun nanofibres and cyclodextrin complexation. The detailed information regarding the nano-delivery of stilbene derivatives is presented in Table 3. The illustration of the applicable delivery system for stilbene derivate is summarised in Figure 2. According to the collected data, there are advantages, limitations, and drawbacks regarding each delivery system, e.g., solubility, permeability, photostability and easiness to scale-up, which are also summarised in Figure 2.

Polymeric nanoparticle

Polymer is a versatile material that is widely employed in drug delivery purposes not only for controlled release formulation but also for tailoring delivery systems. [31] Polymeric nanoparticles are a delivery system that uses the polymer to encapsulate the active moiety to

the core of the particle. In this system, polymer type and characteristics can be utilised and modified extensively to achieve the intended effect. Interaction between drug and polymer or poly-polymers governs a fundamental role in polymeric nanoparticle preparation.[28] Several reported studies showed that polymeric nanoparticles could be applied for the delivery of stilbene derivatives. They have a profound effect on solubility enhancement; thus, bioavailability as well as the antioxidant potency were increased significantly. Encapsulation of compounds into polymeric nanoparticles provides better protection from ambient exposure.[9]

Encapsulated RSV with hyaluronic acid polymer-based nanohydrogels increased the solubility and antioxidant activity of RSV due to reducing its particle size below 250 nm. Antioxidant activity of RSV was higher 1.5 times than that of astaxanthin. However, this finding confirmed that the length of the storage and preparation process reduced the antioxidant activity of RSV.[32] Moreover, the encapsulation of RSV using poly-ε-caprolactone through antisolvent technique was successfully enhanced the thermal-oxidative properties by 2.51 times higher than that of unencapsulated RSV.[33] A similar study reported that RSV was also encapsulated and obtained particle size around 250 nm that improved potential activity on immunostimulant and enhanced lung bioavailability.[34]

RSV encapsulated into the nano-polymeric system along with chitosan (CS) and γ-poly glutamic acid (γ-PGA) through an ion gelation technique increased the solubility of RSV 4.2-fold. γ-PGA, which is a hydrophilic polymer, can improve solubility. Meanwhile, CS, which has mucoadhesive properties, can enhance the absorption of RSV. In addition, it was proved by increasing the absorption of RSV by 1.5-2.0 times higher than that of the non-nano polymeric system. This system not only enhances bioavailability but also provides better protection against photodegradation. CS, a cationic polymer, had significant consideration in the formation of nanoparticles through electrostatic interaction with γ-PGA.[7] This interaction plays a fundamental role in forming the encapsulation system, and thus, it can be applied for the stability and potency enhancement of stilbene derivatives.

In addition, protein is also to be utilised for the preparation of nanoparticles. RSV loaded into polymeric nanoparticles using pea protein isolate through cross-linking technique was induced by calcium ion. This interaction was modulated by increasing the degree of grafting and cross-linking during the formation of polymeric nanoparticles, and hence, it can increase the solubility of RSV. Antioxidant activity of RSV was also increased in a range of 1.1 to 1.4-fold.[35] RSV was nano-encapsulated by kafirin protein and hydrophilic casein protein, which could improve the solubility and had great protection of RSV against photolysis. In

addition, casein was able to slow down the degradation of RSV. The antioxidant activity of RSV was also increased by 1.2 to 1.9-fold.[9] Zein protein nanoparticles could be applied for PTS encapsulation stabilised by fucoidan, which was able to increase solubility and protect from photolytic degradation. Zein protein comprises non-polar amino acids and polar amino acids, but it has low solubility. Thereafter, it required to be complexed along with hydrophilic polysaccharides, namely fucoidan, to increase solubility.[36] In addition, the zein protein has amino acid residues along with double bonds. Hence, it is responsible for providing physical or chemical protection against UV radiation.[37] However, among all nanoparticle preparations, they are limited in scale-up ability due to bulkiness on the preparation process and difficulty to transform in conventional formulation regarding the physical stability of polymeric nanoparticles during the drying process.

Lipid-based formulation

Generally, lipid-based formulation involves micellar, nanoemulsion, liposomes, nanostructured lipid carriers and solid lipid nanoparticles.[38] However, since five years ago, nanoemulsion and solid lipid nanoparticles (SLN) have been frequently employed for the delivery of stilbene derivatives. Nanoemulsion provides better drug loading than SLN. Meanwhile, the stability of SLN was higher than that of nanoemulsion. Generally, nanoemulsion consists of an oily droplet, surfactant and co-surfactant. It can be prepared according to the required energy, namely high energy input methods, e.g., ultrasonication, high-pressure homogenisation or low energy method, e.g., inversion phase or self-emulsification.[39],[40] Meanwhile, the SLN can be prepared by reducing the particle size through a hot emulsification technique or ultrasonication.[41] Both of those systems can increase the solubility through intraluminal solubilisation behaviour and provide better protection against photodegradation. In addition, it can change the transport mechanism through enterocyte transporter, e.g., microfold cell.[42] Thus, it can enhance the bioavailability significantly via a lymphatic pathway.

PTS nanoemulsion prepared by flaxseed oil and Tween 80 was able to increase the bio-accessibility of PTS 4.3 times greater than that of olive oil and Tween 80 (1.1 times). Flaxseed oil produced a smaller particle size than olive oil. Thus it could be easy to be accessible. However, the bioavailability of PTS flaxseed oil nanoemulsion was lower than that of olive oil nanoemulsion because it was related to the nanoemulsion structure affected by fatty acid-containing in oil and its effect on the absorption mechanism.[43]

Nanoemulsion prepared by a combination of triacetin, Kolliphor RH40, and Transcutol as oil, surfactant, and co-surfactant, respectively, was able to increase the solubility of RSV 3-4 fold. In addition, a terpene compound, eugenol, was also incorporated, and it was able to increase RSV permeation in the stratum corneum 1.1 times, whereas the permeation through epidermis, dermis and follicles increased 2.5 fold.[44] An increment of permeation of 1.7 fold was also achieved in RSV incorporated into nanoemulgel prepared by Sefsol 218, Tween 80, and PEG 400 as oil, surfactant, and co-surfactant. The RSV nanoemulgel formulation could increase the antioxidant enzyme levels of CAT and SOD by 1.2-fold compared to conventional gel formulation.[45] RSV nanomicellar system along with Comriptol ATO and surfactants (Poloxamer 188 or Poloxamer 407) increased the antioxidant capacity. This formulation could enhance the CAT and SOD by 1.5 and 1.6 times, respectively, compared to RSV suspension. In addition, it reduced the glutathione level by 1.6-times greater than RSV suspension. A combination of Poloxamer 188 and Poloxamer 407 could increase the efficiency of drug release by 1.6 times higher compared to a single surfactant system.[46] RSV incorporated into SLN reduced the permeation by 1.9-fold, and it was lower than RSV in conventional gel formulation. However, the antioxidant activity was higher 1.09 and 1.13 times compared to RSV in conventional gel and ascorbic acid, respectively.[47]

Coconut oil-based nanoemulsion containing RSV was successfully formulated and enhanced the brain targeting the delivery of RSV via the intranasal route. It showed the bioavailability enhancement by 2.1 times higher than that of RSV suspension.[48] On another side, RSV was also combined with another flavonoid, e.g., quercetin, in the formulation of self-nanoemulsion to enhance the bioavailability by 3-fold and synergistic effect without any interference of biological activity.[49]

Nanocrystals

Nanocrystals are nano-sized crystals lattice structures of drugs stabilised by surfactants or polymers to prevent crystal growth.[50] It can enhance the supersaturation solubility of a drug as well as its bioavailability or antioxidant activity, particularly for poorly water-soluble stilbene derivatives. RSV nanocrystals stabilised by Tween 80 and Kolliphor P188, which was prepared by a wet milling technique, could increase supersaturation solubility of 13.2 and 10-folds, respectively. Therefore, it could enhance the bioavailability dramatically if there was no problem in the absorption process and transport mechanism.[29] Trans-RSV nanocrystals with

surfactant d-α-tocopherol polyethene glycol 1000 succinate (TPGS), lecithin, Pluronic F127 increased drug release of 6.7-fold.[51]

Electrospun nanofibre

Electro-spun nanofibres are prepared from a polymer solution with electrospinning technology. The molecular dispersion of the drug in the polymeric fibre promotes better solubility as well as it is supported by the higher specific area due to the nanofibre surface structure.[52,53] This delivery system is considered to be suitable for delivering the poorly water-soluble polyphenol, e.g., RSV or PTS.[54] Polymer is the main key for this formulation. Polyvinylpyrrolidone (PVP) is frequently used in the electrospinning technique to produce nanofibre. The solubility of RSV enhanced 21.8-fold due to the amorphous form of RSV incorporated into nanofibre along with PVP and hydroxypropyl-β-cyclodextrin (HP-β-CD). This formulation affected the enhancement of RSV concentration in the stratum corneum, epidermis, and dermis than that of RSV. The reported result showed that the antioxidant activity of the nanofibre was equivalent to vitamin C using the ABTS method and even higher in the DPPH method.[55] RSV incorporated into poly-ε-caprolactone nanofibres also increased the solubility by up to fivefold.[56] However, higher solubility is not changing the transport mechanism. Therefore, the precipitation and efflux mechanism is also the main hurdle in nanofibre formulation. However, it is still limited to the scale-up ability due to the requirement of a high voltage instruments and their flexibility.

Cyclodextrin complexation

Cyclodextrins (CD) are cyclic oligosaccharides that have hydrophobic properties on the inner cavity and hydrophilic properties on the outer. Therefore, they can entrap the lipophilic compound inside the moiety followed by hydrophobic interaction. The interaction due to lipophilicity and hydrophobic interaction, as well as hydrogen bonding in the outer side, plays a fundamental role in the complex kinetics. In addition, the hydrophilic outer plays a fundamental role in solubility enhancement.[57] The formation of SD complexes with drugs can increase the solubility as well as their chemical and physical stabilities.[58] RSV-CD inclusion complex provides low protection against photolysis. The amount of RSV in the CD complex was reduced by 25.25% compared to the RSV solution (58.01%). It showed that lower protection against UV was affected by complexation kinetic and unencapsulated RSV.[59]

The formation of β-CD nanosponge using crosslinker, pyromellitic dianhydride can increase the solubility of RSV 5-fold higher compared to RSV suspension.[60] The solubility

increment is due to the expandable structure of the CD nanosponge in water and the complex formation. This system could increase the solubility by 2.5-times. According to the half-time, the CD nano-sponge was able to increase stability by protecting RSV from photolysis 7-fold greater than RSV solution. It was due to the nano-sponge structure, which offered a physical barrier.[61]

RSV-cyclodextrin could form a complex based on metal-organic framework nanocapsules (CD-MOF). The complex could be modified by the addition of a chitosan layer on the CD-MOF (CD-MOF/CS) surface for reducing the aggregation. Therefore, it resulted in a compact structure with resistance to photolysis. The antioxidant activity of RSV can be enhanced by CD-MOF/CS encapsulated due to direct protection from light. Modified layered structure with chitosan also improved the absorption capability.[62]

Conclusion and Future Perspective

The most frequently applied and useful stilbene derivatives, RSV and PTS, can be found in grape seeds, skins and stems and fruit bark skin respectively. To date, nano delivery stands as an attractive procedure meant to help increase the solubility, stability and antioxidant activity of RSV and PTS as well as oral bioavailability and percutaneous or oral permeation. The different delivery systems boost the ability to achieve the intended effect according to the offered features and properties of select delivery systems of stilbene derivatives. Proper selection of a delivery system for stilbene derivate poses a decision that must balance between significant advantages and drawbacks. This review provides further suggestions and perspectives for developing the most frequently applied and potent stilbene derivatives. Polymer-based nanoparticles and nanoemulsions are the most feasible delivery system for RSV and PTS. They offer the most potential features in enhancing solubility, permeation, the potential for antioxidant activity, and the photostability of stilbene derivatives. However, due to feasibility in the manufacturing process, the self-nanoemulsion was the best choice due to its ease to scale up in the manufacturing process compared to the polymeric nanoparticle.

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Ethical Issue

Not Applicable

Declaration of interest

All authors declare that there was no conflict of interest.

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Figure caption

Figure 1. Molecular structure of stilbene building block (a) and stilbene derivatives e.g. resveratrol (b) and pterostilbene (c).

Figure 2. The applied nano delivery and the functionality of the delivery system of stilbene derivatives. * = limited in the feature of delivery system

Figure 1.

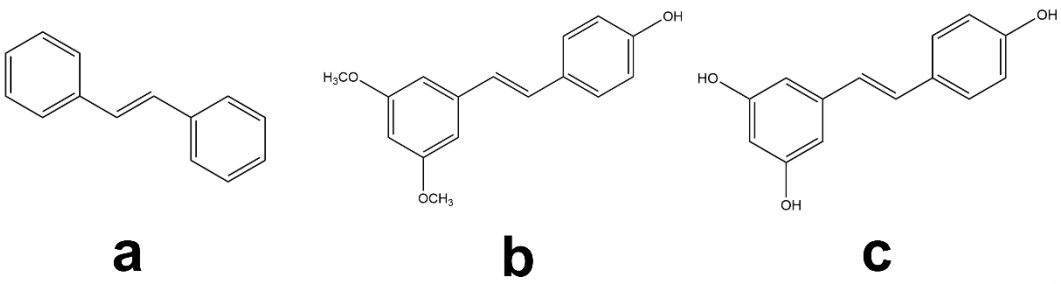

Figure 2.

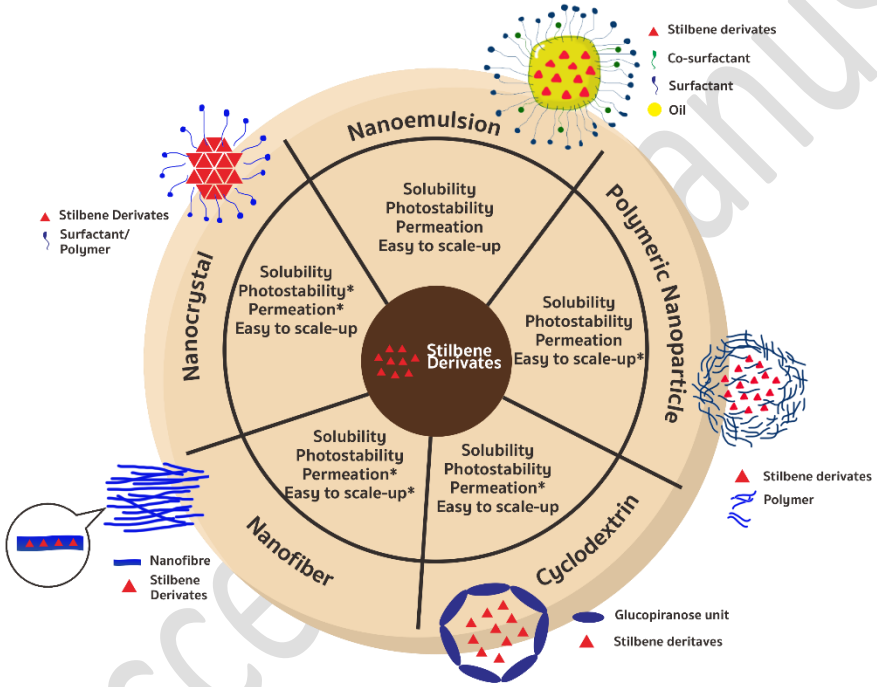

Table 1. Sources of stilbene derivatives as potential antioxidant compounds

Derivate Stilbene	Source (Ref)
Pterostilbene (PTS)	*Salacca plants* [18], thorny palm skin (*Salacca edulis*), Noni Extract (*Morinda citrifolia L*) [19], Lychee (*Litchii chinensis* Sonn.) [63], Blueberries [64,21], Rose[65], Indian Kino *(Pterocarpus marsupium)* [22,20]
Resveratrol (RSV)	Vegetable Hummingbird *(Sesbania grandiflora)*, Snake Fruit *(Salacca zalacca)* and Indian Acalypha *(Acalypha indica)* [66], Korean Peanut (seeds & sprouts) [17], Kakadu Plum [67], Grape [68,14], Propolis extract [16], Jamun (*Syzygium cumini L.*), Jackfruit (*Artocarpus heterophyllus*) and Mulberry (*Morus rubra*) [5]
Trans-RSV	Vine Cane [15]
3-hydroxy PTS	*Sphaerophysa salsula* [13]

Table 2. Antioxidant activity of stilbene derivatives compounds

Stilbene derivatives	**Method (ref.)**	**Potential antioxidant activity**
Resveratrol (RSV)	DPPH [16,69,25,5]	29.36–80.51 mM trolox equivalent (TE), 1.32–3.33 mM gallic acid equivalent (GAE), and 50% inhibition concentration (IC_{50}) 0.07–0.93 mg/mL.
	ORAC assay [70,6]	0.05–3.67 mM TE
	FRAP [6,69]	0.47 mM TE and 30.63–171.33 mM ascorbic acid equivalent (AAE)
	ABTS [6]	1.57 mM TE
	ß-carotene bleaching test [25]	52.50% inhibition
	MAO enzyme kinetic assay [26]	IC_{50} mono amin oxidase (MAO)-A 0.313 µM IC_{50} MAO-B 15.8 µM
Oxyresveratrol	ORAC assay [6]	3.35 mM TE
	ABTS [6]	2.04 mM TE
	FRAP assay [6]	0.52 mM TE
Pterostilbene (PTS)	ORAC assay [22,70,6]	0.03–14.34 mM TE
	DPPH [22,25]	IC_{50} 8.13 µg/mL
	ABTS [6]	1.13 mM TE
	FRAP assay [6]	0.05 mM TE
	ß-carotene bleaching test [25]	Inhibition 23.57%
	MAO enzyme kinetic assay [26]	IC_{50} MAO-A 13.4 µM IC_{50} MAO-B 1µM
Pinostilben	ORAC assay [70]	0.05 mM TE
Pinosylvin	ORAC assay [6]	1.71 mM TE
	ABTS [6]	1.23 mM TE
	FRAP assay [6]	0.31 mM TE

Table 3. The various applied delivery system in stilbene derivatives

Delivery System	Stilbene Derivate	Additive Material	Brief Concept	Finding	Ref.
Polymeric Nanoparticles	Resveratrol (RSV)	Hyaluronic acid	Encapsulation of RSV with hyaluronic acid-based nano hydrogel increased the solubility and antioxidant activity.	The particle size was less than 250 nm and the antioxidant activity was 1.5 times greater than that of astaxanthin. The antioxidant activity of RSV was reduced by 23% when it was incorporated into the nano hydrogel.	[71]
	RSV	Chitosan and γ-polyglycolide (PGA)	Encapsulated RSV by chitosan and γ-PGA increased the solubility, stability, and absorption.	The solubility increased 4.2 times. The rate of degradation slowed down and no cis-RSV was observed. RSV absorption increased 1.5–2 times.	[7]
	RSV	Pea protein isolate (PPI)	Preparation of RSV nanoparticles through ion gelation with PPI induced by $Ca2^{+}$ increased the antioxidant activity.	The antioxidant activity increased 1.1 and 1.4 times in DPPH and ABTS assays, respectively.	[35]
	RSV	Kafirin and casein	Encapsulated RSV by kafirin and casein increased the antioxidant activity and stability.	Antioxidant activity increased 1.2–1.9 times using the DPPH assay. Encapsulation reduced the degradation of RSV.	[9]

	Pterostilbene PTS)	Zein and fucoidan	Zein-fucoidan composite nanoparticles increased the stability and solubility of PTS.	Zein was able to inhibit degradation. Zein/fucoidan nanoparticles increased the solubility and controlled the PTS release in the gastric.	[36]
Lipid-Based Nanoparticle	RSV	Triacetin, Kolliphor EL, and Trancutol	Nanoemulsion with the addition of eugenol increased the solubility, distribution and stability of RSV.	Solubility increased 3–4 times. The addition of eugenol increased the permeation of RSV of 1.1 and 2.5 in stratum corneum to epidermis and dermis to follicles, respectively.	[44]
	RSV	Sefsol 218, Tween 80, PEG 400, and Carbopol 940	The incorporation of RSV into nanoemulgel increased the permeation, deposition and antioxidant activity.	Permeation increased 1.7 times. Deposited RSV and the antioxidant activity were increased 1.9 and 0.8 times, respectively. Nanoemulgel maintained super peroxide dismutase (SOD) and catalase (CAT) levels 1.2 times higher than the gel.	[45]
	RSV	Carbopol 940 dan Precirol Atau 5	Delivery of RSV with solid lipid nanoparticles (SLN) increased the permeation, deposition and antioxidant activity of RSV.	The total permeated RSV in SLN was 1.9 times lower than that of gel. Deposited RSV in SLN was 3.5 times higher than that of gel. The DPPH inhibition of RSV SLN was 1.13 and	[47]

				1.09 times higher than that of ascorbic acid and RSV in gel, respectively.	
	RSV	Compritol 888, Poloxamer 188, Poloxamer 407	CompritolATO-based RSV colloidal carries increased drug release and antioxidant activity.	The drug release increased 1.6 times. CAT, SOD and GSH levels were 1.6 times greater than that of resveratrol in suspension.	[46]
	PTS	Flaxseed Oil- Tween 80 Olive Oil-Tween 80	Delivery of PTS with nanoemulsion increased the bioaccessibility and bioavailability.	The bioaccessibility and bioavailability of PTS increased four times.	[43]
Cyclodextrin Complexation	RSV	Lecithin and Tween 80	RSV-cyclodextrin inclusion complex in lecithin-Tween 80 nanoemulsions enhanced the protection of RSV against degradation and increased the antioxidant activity	Degradation of RSV was 2.3 times more negligible. The antioxidant activity increased 1.35 times compared to ascorbic acid.	[59]
	RSV	Chitosan	The encapsulation of RSV on CD-MOF/CS nanocapsules increased the solubility, stability and antioxidant activity.	The antioxidant activity using the DPPH assay increased 1.1−1.3 times.	[62]

	RSV	β-cyclodextrin, pyromellitic and propylene glycol	The delivery of RSV with hydrogel-based cyclodextrin nanoparticles increased the permeation and stability.	The permeation and photostability of RSV increased 2.5 and 7 times, respectively.	[61]
Electrospun Nanofibre	RSV	Polyvinylpyrrolidone (PVP) and hydroxypropyl-β-cyclodextrin (HP-β-CD)	PVP and HP-β-CD electrospinning nanofibre increased the solubility, antioxidant activity, and penetration through the skin.	The Solubility increased 21.8-fold. The inhibition of the system was higher than that of ascorbic acid. The concentration of RSV in nanofibre was higher in the stratum corneum, epidermis, and dermis than plain RSV.	[55]
	RSV	HPMC, poly-ε-caprolactone (PCL)	HPMC-PCL nanofibre increased the solubility of RSV.	The RSV solubility increased fivefold.	[56]
Nanocrystal	RSV	Polysorbate 80	RSV nanocrystals increased the solubility and penetration through the skin.	Solubility increased 13.2 times. RSV nanosuspension was detected in each layer of the dermis compared to suspension.	[29]
	RSV	Kolliphor RH40	RSV nanocrystal increased the solubility and penetration through the skin.	Solubility increased 13 times. RSV in nanosuspension could penetrate twice that of coarse suspension.	[29]
	RSV	δ-α-Tocopherol polyethylene	Nanocrystal maximized the RSV release and increased the stability.	The RSV release increased 2.26-fold. RSV loss during three months of storage was 1.86% under controlled conditions.	[51]

		glycol 1000 succinate (TPGS), lecithin, Pluronic F127			