CHAPTER 3: BIOACTIVE AND EXCIPIENTS PROFILE

3.1 Profile of Bioactive "Resveratrol"

Resveratrol, also known as 3,5,4′-trihydroxy trans-stilbene is a naturally occurring polyphenolic compound, mainly originates from berries, grapes, and red wine (Arora & Nanda 2019). It has been reported to show potent antioxidant, anti-inflammatory, anti-proliferative and anti-cancer effects. "Resveratrol (3,5,4′-trihydroxy trans-stilbene)" is a natural polyphenolic and a phytoalexin compound. It is a member of the "stilbene family of phenolic compounds". Its prime sources are "grapes, nuts, wine, grape juice, cranberries, mulberries, cranberry juice, and peanuts" (Chedea et al. 2017). It is produced by these plants as a response mechanism to injury and scratch.

Structurally, it is characterized by "two benzene rings linked through isopropyl moiety separated by a double bond". The chemical structure of Resveratrol is shown in Figure 3.1.

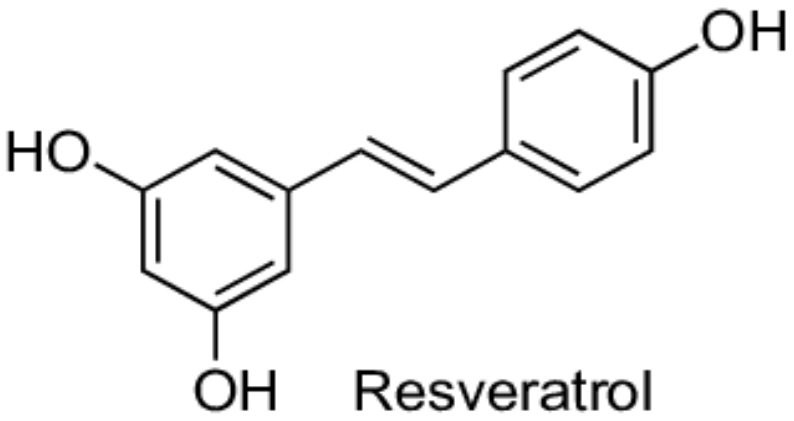


Figure 3.1: Structure of *trans* Resveratrol

It is a well known "activator of the protein deacetylase sirtuin (*SIRT*) gene" in mitochondria, due to which it shows potential anti-aging, anti-inflammatory, and anti-proliferative activity resulting in a modification in "gene expression and intonation of numerous metabolic pathways" (Ruivo et al. 2015). Thus, it offers several systemic as well as topical "biological effects, such as anticancer activity, anti-aging effect, antioxidant activity, cardioprotective, anti-inflammatory activity" as described in Figure 3.2 (Yang & Meyskens 2005; Pangeni et al. 2014). Along with this, it is also effective in

the treatment of several neurodegenerative diseases and chemotherapeutics. Resveratrol is a well-known nutraceutical compound and is marketed over the counter (OTC) as a dietary supplement. In the last few years, it has attained much larger popularity and concerns and is used as a well-accepted food/nutritional supplement.

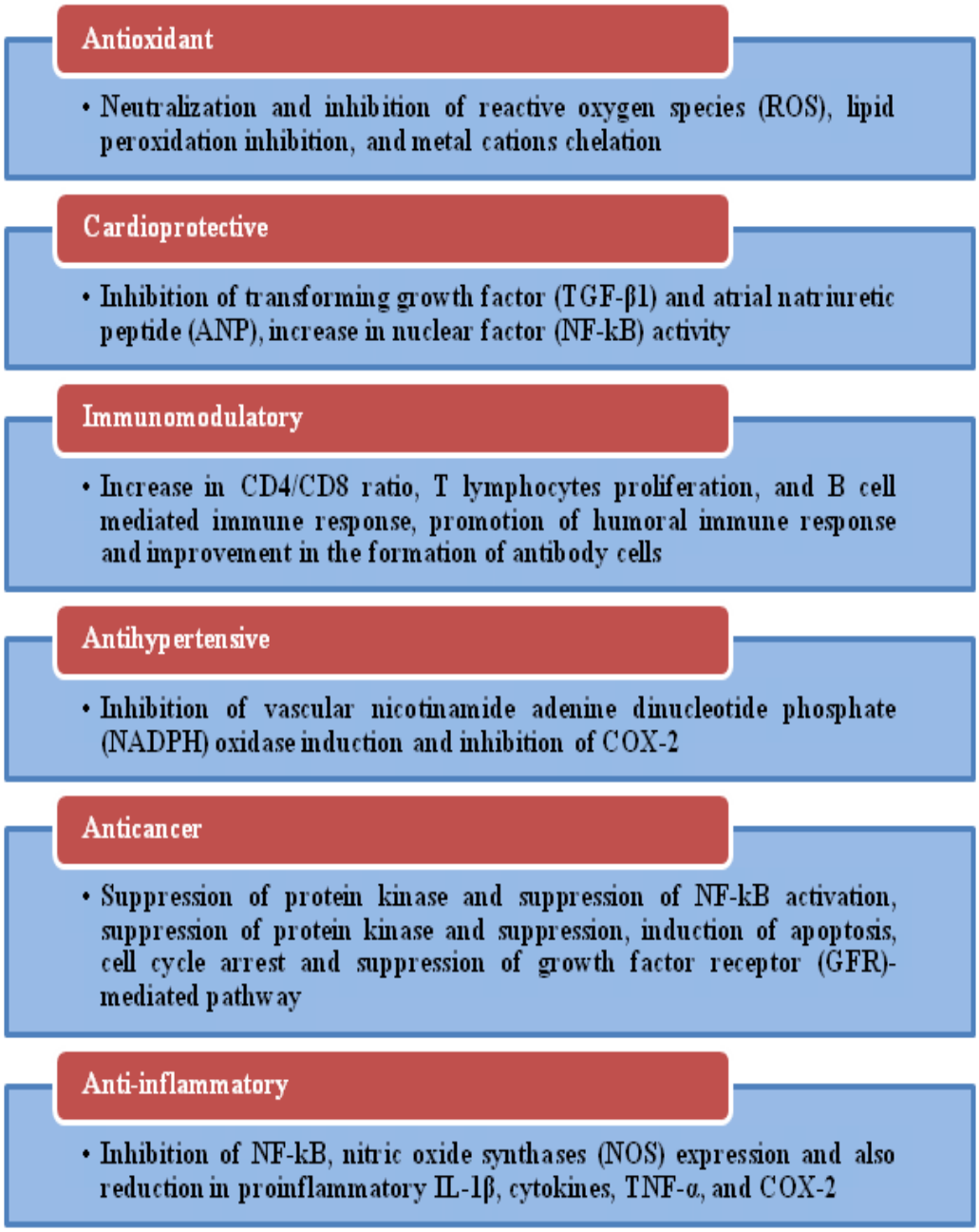


Figure 3.2: Biological roles of Resveratrol with its mechanism of action

3.1.1 Mechanism of action

Resveratrol has several biological roles as described in Figure 3.2 with its associated mechanism.

"Anti-inflammatory potential of Resveratrol results in scavenging of free radicals and thus helps in treating psoriasis-like skin condition". Resveratrol has very low oral bioavailability. Resveratrol is also known to increase the levels of first-line antioxidant defense systems present in the body.

"The oral bioavailability is less than 1% because of extensive and fast metabolism in intestine and liver leading into sulfate and glucuronide metabolites". Thus to avoid hepatic first-pass metabolism and to achieve its dermatological benefits to the fullest, it is highly desirable to deliver it at the local target site.

The following Table 3.1 is given to represent the physical properties of Resveratrol.

Molecular formula	**$C_{14}H_{12}O_3$**
Molar mass	**228.24 g mol^{-1}**
Appearance	**white powder with slight yellow cast**
Melting point	**261 - 263°C / 501.8 - 505.4°F**
Solubility in water	**0.03 g/L**
Solubility in DMSO	**16 g/L**
Solubility in ethanol	**50 g/L**
λ_{max}	**304nm (trans-resveratrol, in water)** **286nm (cis-resveratrol, in water)**

Table 3.1: Physical properties of Resveratrol

3.2 Excipients Profile

3.2.1 Co-surfactant (Transcutol-P)

It is a commonly used component in a cosmetic product and other over the counter topical formulations. It is quite safe and has been applied in several commercial preparations. It has been used in formulations as a co-surfactant and a penetration enhancer. According to literature "it is also used as an ingredient in nanoemulsions, sunless tanning products, and in a wide range of hair-coloring products which are rinse-off. This solvent will be a key component of many cosmetic products as well as dermatics in foreseeable future".

Table 3.2 represented the profile of Transcutol-P used. In the present study, Transcutol P was used as a cosurfactant.

Chemical name	**Diethylene glycol monoethyl ether**
Molecular formula	**$C_6H_{14}O_3$**
Molecular structure	
Molar mass	**134.17 g/mol**
Appearance	**Liquid**
Odor	**Characteristic odor**
Color	**Clear**
HLB value	**4.2**
Solubility	**Soluble in methanol and water**
Toxicity to animals	**Acute oral toxicity (LD50): 10502 mg/kg by oral and 4000 mg/kg by intravenous route in rats.**

Table 3.2: Profile of Transcutol-P

3.2.2 Surfactant (Tween 80)

Tween 80 (polysorbate) is a commonly used non-ionic surfactant/ emulsifier in the food and cosmetic products. It is an approved excipient and reported as safe for human use for both external and internal use.

Table 3.3 represented the profile of Tween 80.

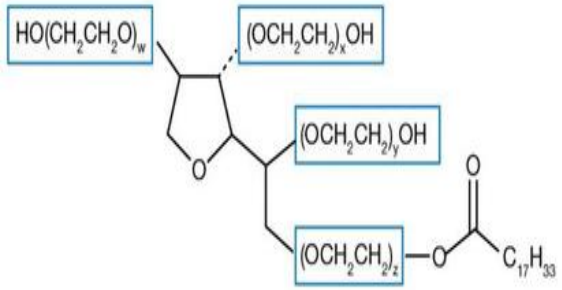
Chemical name	**Polyoxyethylene sorbitan monooleate**
Molecular formula	**$C_{64}H_{124}O_{26}$**
Molecular Structure	
Molar mass	**1310 g/mol**
Formula	**$C_{64}H_{124}O_{26}$**
Density	**1.06–1.09 g/mL, oily liquid**
Physical state and appearance	**Liquid (oily liquid)**
Solubility	**Very soluble in water, soluble in ethanol, cottonseed oil, corn oil, ethyl acetate, methanol, toluene**
Odor	**Fatty (slight)**
Color	**Clear amber, yellow**

Table 3.3: Profile of Tween 80

3.2.3 Pluronic F-127

Pluronic F-127 is the trade name of Poloxamer – 407 manufactured by the German company BASF. It is a hydrophilic non-ionic surfactant and triblock copolymer consisting of a "central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol".

Table 3.4 represented the profile of Pluronic F-127.

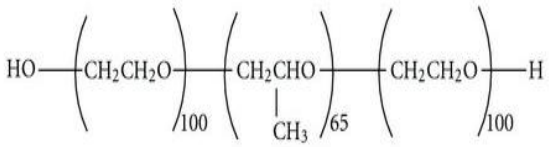
Chemical Name	**Poly(ethyleneglycol)-block poly(propylene glycol)-block poly(ethylene glycol)**
Molecular structure	
Molecular weight	**~12600 g/mol**
Specific gravity	**1.05**
Boiling point	**>100 °C**
Solubility in water at 25°C	**> 10 %**
Viscosity, cps at 77°C	**3100**
Melting Point	**56 °C**
HLB value	**18-23**
Surface tension (0.1% aqueous)	**41 dynes/cm at 25°C**
Form	**Powder**
pH	**6.0 - 7.0**
Water	**≤ 0.75 %**

Table 3.4: Profile of Pluronic F-127

3.2.4 Pluronic P-123

Pluronic P123 is a "symmetric triblock copolymer comprising poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) in an alternating linear fashion, PEO-PPO-PEO." The unique characteristic of PPO block, which is hydrophobic at temperatures above 288 K and is soluble in water at temperatures below 288 K, leads to the formation of micelle consisting of PEO-PPO-PEO triblock copolymers. Some studies report that the hydrophobic core contains a PPO block, and a hydrophilic corona consists of a PEO block.

Table 3.5 represented the profile of Pluronic P-123.

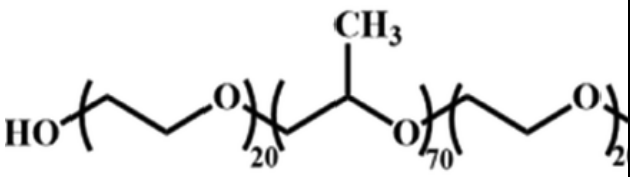
Chemical Name	**Poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol)**
Molecular structure	
Molecular weight	**~5800 g/mol**
Specific gravity	**1.01**
Boiling point	**> 149 °C**
Solubility in water at 25°C	**>10%**
Viscosity, cps at 60°C	**350**
Melting Point	**24.99 °C**
HLB value	**8**
Surface tension (0.1% aqueous)	**34 dynes/cm at 25 °C**
Form	**Paste**
pH	**6.0 − 7.4**
Water	**0.4**

Table 3.5: Profile of Pluronic P-123

3.2.5 TPGS

Vitamin E TPGS has "amphiphilic properties with each molecule consisting of polar hydrophilic (polyethylene glycol) and non-polar lipophilic (phytyl chain of d-α-tocopherol) moieties".

Table 3.6 represented the profile of TPGS

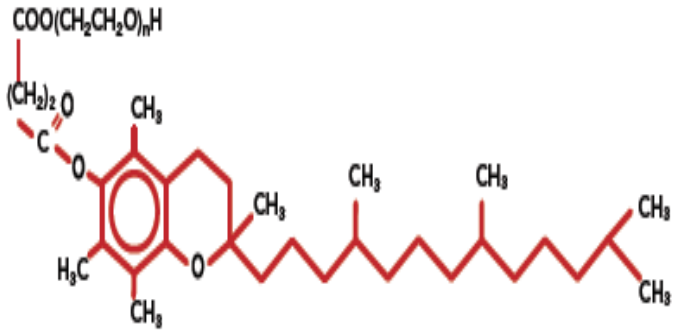
Chemical Name	**d-α-tocopheryl polyethylene glycol 1000 succinate**
Synonym	**TPGS Tocophersolan**
Molecular structure	
Empirical Formula	**$C_{33}O_5H_{54}(CH_2\ CH_2O)n$**
Molecular Weight	**1513 (approx)**
Form	**water-soluble waxy solid**
Color	**White to light tan**
Acid Value	**0.027 meq/g max**
Specific Gravity	**1.06 at 50 °C to 1.03 at 90 °C**
Melting Point	**38 °C (range 37-41)**
Solubility In Water	**~ 20% at 20°C Forms gels between 20 to 90% mixture with water**

Table 3.6: Profile of TPGS

3.2.6 Ethyl oleate

Ethyl oleate is a "fatty acid ester formed by the condensation of oleic acid and ethanol. It is a colorless to light yellow liquid. It is used as a solvent for pharmaceutical drug preparations involving lipophilic substances".

Table 3.7 represented the profile of Ethyl Oleate

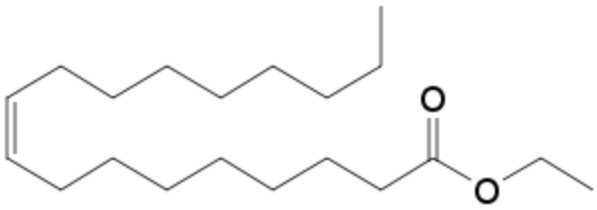
Chemical Name	**Oleic acid ethyl ester**
Molecular structure	
Molar mass.	**310.51 g mol**
Form	**Viscous Liquid**
Color	**Colorless to light yellow**
Density	**0.87 g/cm^3**
Melting Point	**32 °C**
Boiling Point	**210 °C**
Solubility in water	**Insoluble, Miscible in Ethanol, Chloroform, Ether, Fixed oil.**
Acid value	**< 0.5**
Iodine value	**75-85**
Weight per ml.	**0.869 - 0.874g**

Table 3.7: Profile of Ethyl Oleate

3.2.7 Carbopol

It is also known as Poly(acrylic acid) (PAA; trade name Carbomer). It is a synthetic high-molecular-weight polymer of acrylic acid. In the present study, carbomer was used as a gelling agent.

Table 3.8 represented the profile of carbopol.

Chemical name	**Carboxypolymethylene**
Empirical formula	**$(C_3H_4O_2)x$ (-C_3H_5 sucrose)**
Grades	**907, 910, 934, 934P, 940, 941, 971P, 974P, 980 & 981.**
Molecular weight	**Between 1106 and 4106 g/mol**
Description	**White, fluffy, hygroscopic solid powder with a slight acidic odour**
Density (bulk) and (tapped)	**1.76 g/cm^3 and 1.40 g/cm^3**
pH	**2.5 - 3.0**
Melting point	**Decomposition occurs at 260 °C**
Solubility	**Practically soluble in water, and after neutralization in ethanol (95%) and glycerin**
Safety	**It is non toxic and non irritant and there is no evidence of allergic reactions or hypersensitivity in humans.**
Applications	**It is used as suspending, thickening, emulsifying and gelling agent.**

Table 3.8: Profile of Carbopol