International Journal of Advanced Biotechnology and Research (IJBR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-8, Issue-2, 2017, pp1516-1544
http://www.bipublication.com

Review Article

Resveratrol –The Nutraceutical, Whose Real Time Has Come: A Systematic Review

[1]Anita V.Handore and [2]*Sharad R.Khandelwal
[1] (Ph. D Student), Department of Mirobiology,
HPT Arts and RYK Science College, Nashik -422005, MS,India.
avhandore@gmail.com contact No .9881685797, Fax: NA
[2]* Professor, Department of Mirobiology,
HPT Arts and RYK Science College, Nashik -422005, MS,India.
*Corresponding author: Email: Sharad_khandelwal13@yahoo.com, Contact No.9881121023,
Fax: 02532573097, Department of Mirobiology, HPT Arts and RYK Science College,
Nashik -422005, MS, India

ABSTRACT:
Resveratrol, a naturally occurring phytoalexin is emerged as a potent molecule due to its outstanding biological properties. Plants containing such phytoalexins have been effectively used for more than 2000 years in the traditional medicinal preparations like *Drakshasava* made from *Vitis vinifera*. .Applications of resveratrol in nutraceutics, cosmetics and pharmaceutics leads to high demand forits large scale production. This review focuses on the ability of fungal as well as chemical elicitors for enhancement of resveratrol. It also highlights the natural biosynthesis of resveratrol with respect to the grapevine. This review presents an overview on significance of grapevine plant for natural production of resveratrol by use of various biotic and abiotic elicitors in order to achieve the maximum induction and/or elicitation of resveratrol in the grapevine and its cell suspension. In this review, we summarize the limitations of resveratrol with respect to its bioavailability and pharmacokinetics along with ecofriendly possible solutions. In upcoming future, resveratrol would eventually emerge as a promising and cost effective nutraceutical for management and treatment of various diseases and disorders to achieve the desirable target of WHO's Global Action Plan (Yr.2013-2020) of mortality reduction for cancer, cardiovascular diseases, neurodegenerative disorders, diabetes and chronic respiratory diseases etc. Researchers are trying to develop cost effective techniques to enhance the bioavailability of resveratrol. The emerging evidence of nano formulations has given the best success in the digestive processes which ultimately increases the tissue absorption without affecting the activity of resveratrol. Therefore, application of nanotechnology to improve the quality, potency and bioavailability are in the path of success so that the large scale production would help to overcome the disorders.

Keywords: Resveratrol, Nutraceutical, *Vitis vinefera*, Elicitor, Pharmacokinetics, Nano formulations, Bioavailability

1.0 INTRODUCTION
Resveratrol (3,5,4'- trans-hydroxystilbene) is a polyphenolic compound that belongs to the stilibene family. [1].It does not enjoy a wide distribution in the plant world,and has been reported in few fruits and vegetables employed for human consumption. It is a pivotal molecule in plant biology with homologies extending into the realm of mammalian fatty acid metabolism.It's main significance lies in it's role as parent molecule of a family of polymers given the name

viniferin.This compounds is able to inhibit fungal infection ,a property which has earned its inclusion in the class of plant antibiotics known as phytoalexins. [2].Resveratrol is a compound of highly lipophilic and hydrophilic properties and assumed to be more effective than certain other antioxidants like vitamin C and E [3]the trans isomer of resveratrol is stable under high air humidity up to 75% and temperature about 40 ºC [4].Chemically, resveratrol ($C_{14}H_{12}O_3$) is a white powder with a slight yellow cast having a molecular weight of 228 .24 g $mol^{-1}$and melting point of 253 – 255 ºC. It's solubility in water is 0.03 g/L whereas in DMSO, it is 16 g/L and 50 g/L in ethanol.[5].

Resveratrol can be found in free (aglycone) or glycosylated form (piceid) and its oxidative dimerization leads to the formation of its polymer, the viniferins [6]. Both aglycone and piceid exists in cis- or trans- isomeric forms, because their two phenol rings (linked by a styrene double bond) generate the more stable form, trans-resveratrol; but, due to UV photo-isomerization, trans-resveratrol is converted to cis-resveratrol [7].Cis-resveratrol shows maximum of absorbance at 286 nm, whereas the maximum absorbance for isomer trans is achieved at 306 nm. Both the cis or trans isomers are extremely light sensitive and when protected from light, trans-resveratrol is stable for at least 28 days in buffers with pH ranging from 1 to 7, while cis-resveratrol is degraded at pH 10 [8] [Fig.1].

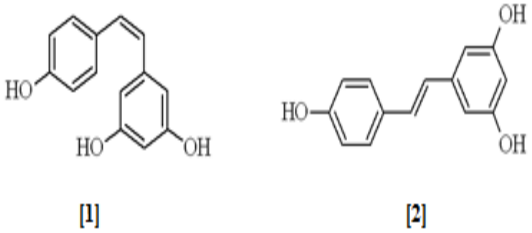

Figure 1. Chemical structures of 1.cis- ((Z)-resveratrol and 2. trans-resveratrol ((E)-resveratrol

1.1. Biological Significance of Resveratrol in Plants

Biological significance of resveratrol in plants is related to an environmental defense mechanism and this key phenotype can help researchers to better understand the properties of resveratrol [9].Several studies have demonstrated that resveratrol is produced in response to biotic and abiotic challenges [10,11] .However, the toxic effect on plant-pathogenic fungal organisms is the outstanding purpose of resveratrol in plants .[12,13].Therefore, when hyphae penetrate through the epidermis of the plant, it promotes the production of proteins and carbohydrates that elicit a plant response. Thus, the plant reacts blocking or delaying the advancement of the invader microorganism producing antifungal compounds such as resveratrol,which acts as a phytoalexin [14,15,16] Similarly, cell-wall hydrolysates of pathogens were effective to elicit a similar response .The rapid accumulation of these phytoalexins in the vicinity of the pathogen attack is critical for plant defense . Furthermore, there is a strong correlation between the tolerance of fungal strains to phytoalexin and their pathogenicity on the plant host [17]

1.2. Biosynthetic Pathway of Resveratrol

Resveratrol biosynthetic pathway consists of four enzymes: phenylalanine ammonia lyase (PAL), cinnamic acid 4-hydroxylase (C4H), 4-coumarate: CoA ligase, (4CL), and resveratrol synthase, also known as stilbene synthase (STS).Only plants with STS, the last enzyme in the resveratrol biosynthetic pathway are capable of synthesizing resveratrol [18].Resveratrol is derived from shikimate-phenylpropanoid and/or polyketide pathway [19].The plant shikimate pathway has two end-products that are the entry to the biosynthesis of phenylpropanoids: phenylalanine and tyrosine [20]..Resveratrol is formed on the phenylalanine/polymalonate pathway, being the last step of this biosynthesis pathway, and can be synthesized either from phenylalanine or tyrosine. Both phenylalanine and tyrosine precursors produce *para*-coumaric acid (*p*-coumaric acid, also known as *para*-hydroxycinnamic acid) [21]*para*-Coumaric acid is generated from phenylalanine through phenylalanine ammonia lyase (PAL) and cinnamate 4 hydroxylase (C4H), which acts in the cinnamic acid intermediate.

Tyrosine ammonia lyase (TAL) exerts its activity directly in tyrosine . [21]. Then, *para*-coumaric acid is activated by ligation to coenzyme A (CoA) by 4-coumaroyl:CoA ligase (4CL) and in the pathway-committing step, stilbene synthase (STS) condenses three units of malonyl-CoA (from fatty acids biosynthesis) with *para*-coumaroyl-CoA, forming a linear tetraketide molecule before a cyclization reaction carried out by STS, generating resveratrol.[22] *trans*-Resveratrol can be modified to *trans*-piceid by 3-O-glucosyltransferase (3-O-GT) [1] [Fig.2].

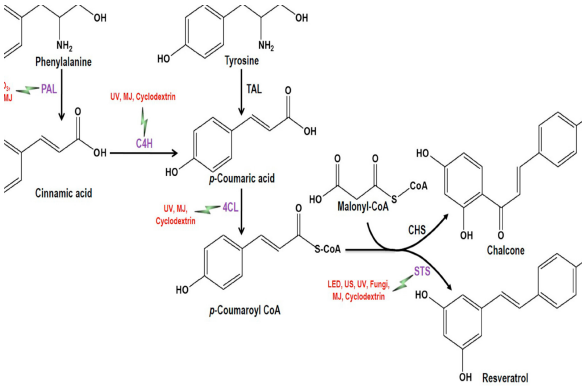

Figure 2. Resveratrol biosynthesis via phenylalanine/polymalonate pathway [23]

1.3. Natural Occurrence of Resveratrol

This phytoalexin is produced by plants in response to biotic and abiotic stress. Biotic stress includes mainly microbial or fungal infections [24]. It also acts as a defenser in case of nematodes or herbivores attack [21].abiotic stresses results from mechanical injury [25]Ultra Violet and Infrared radiation [24]. Ultrasound, ozone and heat [6].

Resveratrol was first isolated from white hellebore (*Veratrum grandiflorum O. Loes*) by M. J. Takaoka in 1940. [1]. .Later in 1963 it was found in Itadori plant [6].In 1976*trans*-resveratrol was discovered in *Vitis vinifera*(grape vine) by P. Langcake and R. J. Pryce [8].

It is reported that ,resveratrol production by plants is also affected by its treatment with chemicals, such as cupric acid, SA(salicylic acid), jasmonic acid, ethylene, $ALCl_3$ (aluminum chloride) and aluminum sulfate [6]and being a stilbene, resveratrol is a plant-specific natural compound produced by various plant families, including *Vitaceae*, *Dipterocapaceae*, *Gnetaceae*, *Pinaceae*, *Poaceae*, *Fabaceae*, *Leguminoseae* and *Cyperaceae* [21] and at least in 72 plant species [27] Resveratrol can be found in grapes and grape products , peanuts, several types of berries (cranberries, bushberries, blueberries and strawberries) [28] ,ferns [22], pines, legumes [25],pistachios [29] also in flowers and leaves (such as eucalyptus, spruce, butterfly orchid and rheum) [27].

2.0.Grapevine as a source of Resveratrol

Although there are various natural sources of resveratrol,*Vitis vinefera*(grapevine), one of the ancient and most widely cultivated fruit crop in the world is considered as important dietary source of resveratrol.In the late eighties the interest of the scientific community towards grapevine have been increased because of the epidemiological studies showing an inverse relationship between moderate wine consumption and risk of coronary heart diseases ,the so called 'French Paradox' and since then, grapes and wine have been in the spotlight. [30].Different research groups have undertaken the study of grape metabolomics and revealed the rich profile of grape including rich source of polyphenolic compounds including resveratrol which is implicated in important biological functions of the body .In recent years, the analyses of grape composition and its effect on human health led to the conclusion that resveratrol is one of the key grape compound responsible for the preventive and therapeutic abilities of grapevine.

In 1976, Langcake and Pryce published a paper demonstrating that resveratrol was produced by *Vitis vinifera* as a response to infection or injury". This work was focused exclusively on its effect on disease resistance thereafter resveratrol was studied extensively in grapes for the next 15 years. [31,32,33].

Most interest has centered upon resveratrol in grapevines (*Vitaceae*) because its function as phytoalexin and its role as a marker of infection by various pathogens has been most intensively investigated in this genus , and results appear to hold true for other members of plant world in which similar investigations have been conducted.

[2] .Grapevine stilbene synthase enzymes are produced from large a family of greater than twenty genes [34,35].These genes are differentially expressed in various vine tissues. Resveratrol and other stilbenes are constitutively produced in woody tissues but induced in leaves and berry skins [31 ,32]

In the grape species, this polyphenol reaches concentrations of 50-400 µg/g fresh weight in the leaves.[33]..In 2001,Romero-Perez, A. I *et al* has reported that average amount of trans resveratrol in dry grape skin was 24.06 µg/g .Fruit juices can also be a good source of resveratrol They analysed 36 grape juice samples and found that in red grape juices the average concentration level for trans-resveratrol was 0.50 mg/L and for cis-resveratrol 0.06 mg/L whereas, in white grape juices, 0.05 mg/L for trans-resveratrol, and cis-resveratrol was not detected in any sample [36].In 2004,J. Lachman *et al* determined the contents of trans-resveratrol in grape musts, grape skins and seeds of twelve vine varieties from the harvests 2001 and 2002 and found that the average annual trans-resveratrol values in the years 2001 and 2002 were 0.817.10–2 mg/kg and 4.97.10–2 mg/kg Dry Matter in grape skins , 52.7.10–2 mg/kg and 4.63.10–2 mg/kg Dry Matter in the seeds and there was hardly any trans-resveratrol presence in the must. Many papers have been published describing some approaches for evaluating the concentrations of cis- and trans-resveratrol in several selected wines. [37]. In 2007, Ulrik Stervbo *et al*.,has reviewed the content of resveratrol in red wine and reported that an average red wine contained 1.9 ± 1.7 mg/l (8.2 ± 7.5 lM) trans-resveratrol, with non-detectable levels as the lower limit. The highest levels of trans-resveratrol measured are 14.3 mg/l (62.7 lM) [38].In 2016,Márcia L *et al*. has developed and validated HPLC method for quantifying trans-resveratrol in hydroalcoholic extract of the husks and the found the trans-resveratrol concentration as17.33 µg/mg.

2.1.Factors Affecting Resveratrol Production

Grapevine can biosynthesize and accumulate resveratrol in the berry, stem, axillary bud, shoot tip, petiole, root and leaf .In the grapeberry, resveratrol is synthesized almost entirely in the skin and synthesis peaks just before the grapes reach maturity. The terminal enzymes in the biosynthesis of resveratrol get activated in response to exogenous stress factors such as injury,ultra violet irradiation and chemical signals from pathogen fungi. The level of peak approximately 24h after stress exposure and decline after 42-72 h as a result of activation of stilbene oxidase.[7]. The degree of increase in resveratrol levels in grapes and grape products depend on the variety and stress exposure[39,40]. geographic region, agronomic factors, climatic factors, plant stress conditions, and oenological practices, Fungal pressure, time of harvesting, duration of skin contact during fermentation and degree of maceration of skin**[41].**

The agronomic practice of cluster thinning is commonly recommended to increase fruit quality which has been shown to increase resveratrol production in grape [42].Vineyard altitude may also influence resveratrol production in grapes. 'Malbec' grapes grown at three different sites (500, 1000 & 1500 m.a.s.l.) showed significantly more resveratrol and total polyphenolic production in berries at the highest site This increase in resveratrol was attributed to increased exposure of berries to UVB radiation [43]. In 1994,,L.Bavaresco *et al* found increasedaccumulation of resveratrol with high potassium, along with low levels of nitrogen [44]. It was investigated that pesticides also affects on induced accumulation of resveratrol. It was found that not only grapes treated with pesticides like Quinoxyfen, Fenarimol, Penconazole, Dinocap etc.showed higher amounts of trans-resveratrol accumulationover control but also wine from cv. Campania treated withwettable sulfur (fungicide and insecticide suitable to be used in organic gardens) showed an increased accumulation of trans-resveratrolby 1.6 times, as compared with the control [45].

The study on effect of viticultural and enological methods on resveratrol content of wines showed that wines produced from the grapes exposed to

ultraviolet light prior to processing had significantly higher levels of resveratrol whereas, skin contact time had no significant effects on level of resveratrol and fining agents showed negative effects on level of resveratrol.[46]. Kostadinovic S *et al.*,has studied the effects of time of maceration, type of yeast and the level of sulphur dioxide and that concentration of resveratrol in wine greatly influenced by these important factors [47].

2.2.Fungal Attack

Climate change is a key controlling factor exerting both biotic and abiotic stresses resulting into pathogenic attack including Gray mold diseases caused by Botrytis fungi. ,which is responsible for significant economic damage in vineyards .During last fifty years ,management of *B. cinerea* has relied heavily upon the use of synthetic pesticides. These residues are persisting into different value added grape products and adversely affecting on human health, viticulture and economy of that country.

Biological control agents are becoming increasingly interesting as alternatives to the use of chemical fungicides which are proving hazardous to the environment as well as being responsible in bringing about resistance to the disease.Biocontrol experiments against *Botrytis cinerea* have been attempted by the utilisation of *Trichoderma sp.*[44].*Serratia marcescens*(Akutsu, K *et al*.,1993), *Gliocladium roseum* and *Penicillium sp.*[48] and *Bacillus circulans*[49].

Although,*Botrytis cinerea* was found to be highly pathogenic to the vitroplants (plants grown on sterile media in test tubes) of *Vitis vinifera* and *Vitis rupestris*. The fungus acts as an elicitor towards the formation of resveratrol .It is reported that grapes infected with *B. cinerea* can produce large amounts of resveratrol.[50]. In1976,Langake and Pryce stated that stilbene phytoalexins are formed on the phenylalanine/ polymalonate pathway and accumulates very rapidly in seemingly healthy grape tissues adjacent to *B. cinerea* infected zones. The difference in stilbene-resveratrol production in the leaves and berries was also reported to be correlated with susceptibility to *Botrytis cinerea*[51]. Leaf area infected with *B. cinerea* showed three fold increase in accumulation of resveratrol which is disappeared as the disease advanced further[44].It is reported that considerable high amount of trans-resveratrol was induced by the 2nd day of *B. cinerea* infection which was followed by the rapid decline in the levels by the 5th day after infection[49,52].It is noted that In blooming stage ,leaves, shoots, and flowers showed 4–5 times induced accumulation of resveratrol following three days after *B. cinerea* inoculation[53].

In 1998, Bernard Paul*et al.*,has reported the elicitation of resveratrol by a bacterial strain(genus Bacillus) isolated from soil.He has investigated that the bacterial strain was found to be an antagonist of *B.cinerea*strain.Its attack on the grapevine acts as an elicitor for the production of resveratrol. This compound was also formed when the leaves of the grapevine vitro plants were inoculated with the bacteria alone, and this activity was enhanced when a mixture of the *B.cinerea* strain and the antagonist bacteria was applied.[49]

In another study,it is mentioned that infection with *U. necator* resulted in 12 times higher accumulation of resveratrol in grape skin [14] also grapes infected with *P. viticola* showed 5 times more resveratrol accumulation than healthy grapes [54]. *R. stolonifer* was also found to induce 4 to 8.5 times accumulation of resveratrol in grapes after 24 h of incubation. However, subsequent incubation resulted in gradual degradation of the accumulated resveratrol [55].The localization and concentration reached by resveratrol is critical to inhibit fungal growth .In this regard, it has been demonstrated that the enzyme stilbene synthase, which is a limiting-step enzyme in resveratrol biosynthesis, was predominantly expressed in the exocarp of grape berries, which correspond to the highest levels of resveratrol found in the particular tissue of the berry [56].Altogether, it is observed that resveratrol synthesis is induced in plant tissues under the pathogenic attack, which provides a defense mechanism to counteract pathogen proliferation in the plant. [57].

2.3. Resveratrol Synthesis

There is high demand for resveratrol due to its nutraceutical, cosmetic, and pharmaceutical uses. Resveratrol can be obtained by different methods like,extraction from plants,chemical synthesis,use of biotechnologies [58].In 1941, resveratrol was first time synthesized by Späth and Kromp. [59] since then, the researchers have started to find different pathways to synthesize resveratrol in the laboratory. Synthesis of resveratrol can be carried out by Modified Perkin reactions starting from benzaldehydes and various substituted hydroxyphenylacetic acids [60].,Wittig and Horner-Wadsworth-Emmons condensations between, respectively, appropriate phosphonium ylides [61] or phosphorylstabilized carbanions [62] and aldehydes and Heck reaction, which is a palladium-catalyzed olefination of aryl or vinyl halides well suited for hydroxystilbene synthesis due to its significant chemo selectivity and amenability to a wide range of functional groups. [58].However, there are number of limitations for preparation of resveratrol and its derivatives in large amounts by using plant extraction also, these methods are neither cost effective nor environment friendly. Whereas, advantages provided with plant cell culture systems are: (i) Low production cost (ii) Independent to plant supply due to seasonal fluctuation. ;(iii) No need of raw material stocks ;(iv) Cultures can be scaled up for resveratrol production ;(v) Environment friendly with better social image .

2.3.1.Plant Cells Cultures

Plant cells cultures have been an important source for the production of secondary metabolites and other substances of commercial interest due to an attractive alternative to the extraction of whole plant material because, plant cells are biosynthetically totipotent, each cell in culture retains complete genetic information and hence is able to produce chemicals found in the parent plant .

Besides that, cultured plant cells proliferate in vitro indefinitely – unlike primary animal cells cultures that undergo only a limited number of cell divisions. These systems have several other advantages, such as their independence of geographical and seasonal variations, performance of stereo and region specific bio transformations and an efficient downstream recovery.[63,64].It is found that, plant cell culture is a useful tool for producing active secondary metabolites i.e. stilbene-resveratrol under the controlled conditions. Due to the high level of stilbenes accumulation in grape. Research studies on grape cell cultures has been under taken to investigate different factors that are able to induce and/or modify stilbenes biosynthesis, regulation and metabolism[65].Cell cultures have been established from many plants but often ,they do not produce sufficient amount of the required secondary metabolites. So, for enhanced production of required secondary metabolites, use of elicitors is proved to be a promising technique.

2.3.2.Cell Suspension Cultures

Production of trans resveratrol by cell suspension cultures is the most suitabl method because of the homogeneity of an in vitro cell population, large availability of material, good reproducibility of conditions and high rate of cell growth. In this type of culture, the main advantage is the unnecessary genetic modification of the plant cell, because they are able to produce trans-resveratrol constitutively or in response to stress [1].

In 2014, Phillip Jeandet and his co-workers reviewed the resveratrol production at large scale using grapevine cell culture system and demonstrated the biotechnological production of resveratrol and some of its derivativesthrough plant cell suspensions, such as grapevine cell culture systems by elicitation technique .

It was found that Methyl jasmonate, cyclodextrins, the combination of bothand chitosan are the elicitors leading to the best responses in terms of resveratrolamounts produced in flasks.

2.4. Effect of Elicitors

Grapevine plant is the main dietary source of resveratrol .Enhancement of resveratrol can be

carried out by use of different elicitors such as fungal cell wall fragments[51],CD (Cyclodextrins)[66,67] ,RAMED (Randomly Methylated-β-cyclodextrin) or DIMED (2,6-di-O-methyl-β-cyclodextrin) , sodium acetate, amino acids, sugar or UV-irradiation [1] Na-orthovanadate, laminarin [68] ,Chitin [69], Jasmonic acid and its more active derivative, MeJa (Methyl jasmonate) [70,71,72]. In 1996,Adrian *et al*. has studied the induction of resveratrol in grapevine leaves by treatment with Aluminium chloride [73], In 2006, J.B. Jimenez and his co-workers has studied short anoxic treatments to enhance trans resveratrol content in grape and wine [74].

Cyclodextrins can also be used as a true elicitors, which can induces defense responses including pathogenesis-related proteins and phytoalexin synthesis, especially the stilbenes like trans-resveratrol in the *Vitis vinefera*.[67,75]. Most of the publications concerning secondary metabolite production by means of plant cell cultures reported that elicitation with Methyl jasmonate increases accumulation of secondary metabolites [76,77,70]. Apart from being elicitors, cyclodextrins also protects resveratrol in the medium by complex formation leading to a significant production of resveratrol [1].Although MeJa affects cell growth and does not promote the increase of resveratrol, a combined treatment with MeJa and CD led to an increased accumulation of resveratrol in the medium because they act synergistically, inducing the expression of STS (Stilbene synthase) and the general phenylpropanoid pathway, leading to a marked increase in the resveratrol amount [78].

Belchi-Navarro and his co-workers has studied on enhanced extracellular production of trans-resvertrol in *Vitis vinifera* suspension cultured cells by using Cyclodextrins and Methyl jasmonate.[79]. In 2013,Almagro *et al*., has carried out bio production of trans-resveratrol from grapevine cell cultures and production of grapevine cell biomass and resveratrol in custom and commercial bioreactors using Cyclodextrins and Methyl jasmonate as elicitors.[77]

Ultrasonication technique to increase the accumulation ofresveratrol in grape skins and leaves was first time, applied by Hasan *et al*.

The resveratrol accumulation was found to be increased ingrape skin by 7.7 folds, after treatment with 5 min ultrasonication treatment, followed by 6 h incubation.

However, the increase of resveratrol in leaves was quite less than that in grape skin. The amountof increased resveratrol in grape leaves after 15 min of ultrasonication, followed by 3 h incubation,was 1.8 fold higher than that observed in non-treated control.[80] .

2.4.1. Resveratrol Production System

Resveratrol was successfully produced using hairy root cultures as well as callus culture of *Arachis hypogaea* (peanut) But, the yield of resveratrol production by hairy roots was low i.e . 1.5 mg/gand callus culture showed very low production of resveratrol which was 0.012 mg/g .In vitro resveratrol production was also carried out by use of *Gossypium hirsutum L.* (cotton) where, resveratrol was produced in very low quantity (0.0072 mg/g) .

It is reported that *Vitis vinifera* cell suspension cultures are particularly suitable for resveratrol production, It was found that without any elicitors, cell suspension cultures of *Vitis vinifera* produced 280 mg/L. However, when RAMED was added, the amount of resveratrol increased to 5027 mg/L. It was found that yield of resveratrol production by callus culture of *V.vinefera*was 33mg/g.[1].

Resveratrol production using microorganisms is an alternative to plant cell systems . *E.coli* have been studied for resveratrol production because of its well characterized fermentation properties and genetic tractability where the yield of resveratrol production was 2340 mg/L.[22].

Tobias Sydor *et al*.,2010 showed that *S.cerevisiae* is well suited as a host for industrial resveratrol Production which was 391 mg/L.[81].In *V.vinefera,,* resveratrol production and elicitation can be carried out by using different chemicaland physical methods. [Table.1]

Table.1. Resveratrol Production in *Vitis vinefera* by Using Abiotic Elicitors

Grapevine cultivar (Cell suspension)	**Elicitor**	**Amount of resveratrol**	**References**
In vitro *V.vinefera* culture	$AlCl_3$(0.05%)	97.94µg/g DM resveratrol	[82]
Vitis vinifera cvGamay	MeJA (100 µM)	20 mg/L	[83]
Vitis vinifera cvBarbera	MeJA 10 µM	i)23.94 µg/g DWresveratrol intracellular ii)7.98 µg /g DWresveratrol extracellular	[70]
i.Vitis vinifera cvMonastrell	MeJA(Methyl jasmonate) 5 µM MeJA 100 µM	798µg/g DWresveratrol 3074 µg/g DWresveratrol	[79]
Vitis vinifera cvGamay Fr´eaux var. Teinturier	MeJA 10 µM + SA 500 mM + resin H2MGL	2667 mg/L resveratrol	[84]
Vitis vinifera cvGamay	DIMEB **(Dimethyl**-β-cyclodextrin) , 5 mM	148–184 mg/Lt-resveratrol	[85]
Vitis vinifera cvMonastrell	DIMEB 50 mM HYPROB50 mM CAVASOL50 mM	>4000 mg/L t-resveratrol 5000 mg/L t-resveratrol 5000 mg/L t-resveratrol	[86]
Vitis vinifera cv Monastrell albino	DIMEB 50 mM HYPROB 50 mM G2βCD (6Omaltosylβcyclodextrin)50mM βCD(βcyclodextri) 18 mM Sulfo-βCD 50 mM	3400 mg/L t-resveratrol 3000 mg/L t-resveratrol 650 mg/L t-resveratrol Weak response Toxicity	[67]
Vitis vinifera cvGamay Rouge	DIMEB 50 mM HYPROB 50 mM G2βCD 50 mM βCD 18 mM Sulfo-βCD 50 mM	3000 mg/L t-resveratrol 990 mg/L t-resveratrol 400 mg/L t-resveratrol Weak response Toxicity	[67]
Vitis vinifera cvGamay	Methylated CDs (Cyclodextrin) 50 mM	900 mg/L resveratrol	[83]
Vitis vinifera cvMonastrell	Undefined CDs50 mM	600 mg/L resveratrol	[79]
V. riparia × V.berlandieri *V. amurensis* *Vitis vinifera* cvMerzling *Vitis vinifera* cv Pinot noir	DIMEB 50 mM DIMEB 50 mM DIMEB 50 mM DIMEB 50 mM	911 mg/L resveratrol 225 mg/L resveratrol 4 mg/L resveratrol 0.5 mg/L resveratrol	[88]
Vitis vinifera cvMonastrell albino	DIMEB 50 mM + MeJA 100 µM	365 mg/DWresveratrol	[78]
Vitis vinifera cvGamay	Methylated CDs 50 mM + MeJA 100 µM	3100 mg/L t-resveratrol	[83]
Vitis vinifera cvMonastrell	Undefined CDs 50 mM + MeJA 100 µM	3000 mg/L resveratrol	[79]
Resveratrol Induction using UV irradiation			
Chardonnay (white)	UV 254 10 min, 0.36 J/cm^2,2day	122.9 mg/g	[39]
Napoleon (blue)	UV-C 254 nm 30–510 W, 5 s–30 min (30–60 s opt.) 20–60 cm (40 cm opt.) 3 days storage time (opt.) Napoleon (blue)	114.7–115 mg/g	[87]
Red Globe (blue)	UV-B 302.1 nm resonant wavelength, 0.141 kJ/m^2, 5 ns pulses, 10 Hz frequency, 45 min	21.3 µg/ml extract	[74]
Resveratrol Induction using Ozone			
Thompson Seedless (blue)	Ozone, 8 mg/min, 20 min	11mg/g	[89]
Napoleon (blue)	Ozone, 8 ppm/30 min every 2.5 h 38 days at 0°C	2.81 mg/g	[90]
Superior White	Ozone,3.88 g/h	13.0 mg/g	[91]
Cardinal CL80 (blue)	72 days storage at 5°C	5.00/8.10 mg/g	[92]

3.0. Health Benefits

According to WHO projections, total annual number of deaths from non-communicable diseases will increase up to 55 million by 2030 .However, WHO has aimed to reduce overall mortality from non-communicable diseases like cancer, cardiovascular diseases, diabetes and chronic respiratory diseases by 25%. [93].

Plants containing resveratrol have been effectively used for more than 2000 years in the traditional medicinal preparations like drakshasava the well known Indian herbal preparationor resins of which the main ingredient is *Vitis vinifera L.*[49]

There are number of studies dealing with the ability of grape polyphenols (resveratrol) and red wine to protect against different types of diseases [94] .Over the past few decades, there has been an increasing emphasis on using lifestyle changes and nutritional modifications to prevent and treat the chronic diseases.[95,96].Caloric restriction is an effective means of preventing chronic disease and ultimately increasing lifespan in laboratory animals .However, it is difficult to employ in actual practice, especially considering the cultural emphasis on eating that is a major contributor to many chronic diseases. As such, considerable research has been directed towards identifying such substances which can mimic the physiological effects of caloric restriction, and resveratrol has emerged as a leading candidate in this realm. [97]

Scientific interest in resveratrol has continually gained momentum since 1997, when it was first demonstrated to prevent carcinogenesis in mice [98]. In the intervening years, this molecule has received considerable attention for its anti-inflammatory, anti-tumorigenic, and anti-oxidant properties, as well as its ability to increase lifespan in lower organisms and improve general health in mammals .Multiple mechanisms of action of resveratrol may related to its health benefits.[99].Reports of significant life extension in simpler laboratory organisms, combined with thousands of in vitro and in vivo studies supportsthe role of resveratrol in either the prevention or treatment of chronic diseases can suggests that resveratrol and similar nutraceuticals may have the potential to make an extraordinary impact on human health.[100].

3.1. Anti-Cancer Activity

Resveratrol is such a molecule which has been widely researched for its anti-cancer effects, because resveratrol shares most of its targets with metabolic reprogramming of tumor cells which is a reemerging issue in recent cancer biology. It is found that resveratrol down-regulates the increased glycolytic activity of tumor cells at multiple levels, facilitating apoptosis of tumor cells and inhibiting tumor cell proliferation. Moreover, resveratrol might prevent metastasis and tumor invasion through inhibiting inflammation and angiogenesis.[101]

Anti-cancer effects of resveratrol are thought to have cancer selectivity with minimal toxicity to normal cells. Low pH condition around tumor cells due to increased lactate production from enhanced glycolysis may promote the pro-oxidant anti-cancer activity of resveratrol.[102]. Numerous in vitro studies have shown that resveratrol has multiple anti-cancer effects, protecting against both tumor initiation and cancer progression pathways. For example, resveratrol can promote cell cycle arrest leading to apoptosis of tumor cells, prevent tumor-derived nitric oxide synthase expression to block tumor growth and migration, as well as act as an antioxidant to prevent DNA damage that can lead to tumor formation [103,104]

Resveratrol has been found to inhibit tumor initiation, promotion, and progression in vitro, as well as reduce skin tumor incidence and multiplicity via topical application to mice in vivo [105].It was investigated that resveratrol inhibits cyclooxygenase (COX) activity, which is known to play a role in tumor genesis by converting arachidonic acid to prostaglandins, inflammatory compounds that promote tumor cell proliferation [106,107]. In 2000, Gautam SC *et al*demonstrated that the IC50 of resveratrol for proliferation inhibition was significantly lower for cancer cells as compared to normal cells .[108].

The anti-proliferative activity of resveratrol has been observed in a number of cancer cell lines and may be due, in part, to the induction of apoptosis [109,110,111] .In 2002,Potter *et al* suggested that the anti-proliferative effects of resveratrol on cancer cells is the result of a metabolic conversion of resveratrol to piceatannol by cytochrome P450 1B1 (CYP1B1). CYP1B1 is highly expressed in cancerous tissue of the breast, colon, lung, esophagus, skin, lymph node, brain, and testis, but not in the normal tissue[112].The molecular mechanisms associated with the anti-proliferative effects in cancer cells involve the activation of p53 and the suppression of nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) [113,114]. In 2005,Castello and Tessitore found that proliferation inhibition may also be caused by the arrest of the cell cycle . [115].A study on Female SCID mice with orthotropic inoculation of MCF-7 and MDA-MB-231 breast cancer cells into the mammary fat pad and found that with the oral dose of resveratrol (50–200 mM)for two days,Suppressed cell proliferation with IC50 valuesof 131–187 mM after 24 h; induced cellcycle arrest at G1 and S phases; inhibitedexpression of NF-kB and downregulation ofits anti-apoptotic gene products; inducedapoptosis.. [115,116].

In 2009, Chen J, Dong *et al.*, studied on inhibitory effect of resveratrol on the growth of human colon cancer ls174t cells and its subcutaneously transplanted tumor in nude mice and found decreased expression of anti-apoptotic factor bcl-2, increased expression of apoptotic factor bax and blocked the cell cycle at S phase thus inhibiting the growth of 1s174t cells.[117]In 2010,Vanamala J *et al.*, carried out In vitro study with model,HT-29, SW480 Human coloncancer cell lines and results demonstrated that resveratrol suppresses the colon cancer cell proliferation by increasing apoptosis even in presence of IGF-1. Suppressed IGF-1R/Akt/Wnt signaling pathways and activated p53.[118].Bhattacharya S. *et al*(2011) studied on Mouse model B16F10 and B16BL6 melanoma cells and observed that resveratrol reduced the malignant properties of highly invasive melanoma cells [119].

In 2013,Gokbulut A A *et al* carried out In vitro study of Resveratrol and quercetin-induced apoptosis of human 232B4 chronic lymphocytic leukemia cells by activation of caspase-3 and cell cycle arrest showing the decreased proliferation of human 232B4 CLL cells by inducing cell cycle arrest at G0-G1 phase, Inhibiting cell cycle progression. Induced apoptosisby increasing caspase-3 activity[120]In 2014,Tanu Garg, *et al*., analysed the chemopreventive and chemotherapeutic effects of resveratrol in various types of cancers along with its possible mechanisms and stated that Resveratrol can be used as an adjuvant to other chemotherapeutic agents in various carcinomas[121].

In 2017,.Ariane *et al*., summarizes the known effects of resveratrol and its main metabolites on drug metabolism in order to help characterize which populations might benefit from resveratrol for the prevention of cancer, as well as those that may need to avoid supplementation due to potential drug interactions [122]. David León *et al* has reviewed some alternatives which can be exploited to improve cancer therapies, including the use of other polyphenols, or the combination of resveratrol with other molecules and their impact on glucose homeostasis in cancer and diabetes [123].

3.2.Neurodegenerative Diseases

It is reported that oxidative stress and damage caused by reactive oxygen species (ROS) play a major role in neurodegeneration [201]. Oxidative mechanisms associated with neuroprotective effects of resveratrol was described by Albert Y. Sun *et al*., This study showed that the beneficial effects of resveratrol are not only limited to its antioxidant and anti-inflammatory action but also include the activation of sirtuin1 (SIRT1) and vitagenes, which can prevent the deleterious effects triggered by oxidative stress and also described the mode of action of resveratrol and its application as a potential therapeutic agent to ameliorate stroke damage as well as other age-related neurodegenerative disorders.[202].In 2017,

Squillaro T *et al.*, reviewed nanotechnology-based polyphenol delivery as a novel therapeutic strategy for the treatment of age-related neurodegenerative disorders [203].Thereforeresveratrol has been proven to be a universal remedy,for a wide range of neurodegenerative disorders such as Parkinson's(PD), Alzheimer's(AD), and Huntington's diseases (HD) .

3.2..1. Alzheimer's (AD)

AD is a progressive, age dependent neurodegenerative disorder leading to the most common form of dementia in elderly people. In 2008, V. Vingtdeux *et al* studied the Beneficial effects of resveratrol against Alzheimer's(AD), and stated that resveratrol shows ability to Protects cellular DNA, lipids, and proteins from oxidative damage,it can reduces the toxic effect of reactive oxygen species (ROS)and superoxide anion production .It also decreases the level of nitric oxide (NO) as well as exerts neuroprotection against glutamate neurotoxicity.It can antagonizes[Ca^{2+}] cytoplasmic elevation and neurotoxicity also can stabilizes the levels of antioxidant TRXthioredoxin ,glutathione peroxidase (GPx) glutathione-S-transferase (GST) and reductase(GR) superoxide dismutase(SOD), and catalase (CAT). Furthermoreit shows a moderate antioxidant activity towards the DPPH radical and prevents the lipid peroxidation and low density lipoprotein (LDL) oxidation. [123]. In 2017,Teng Ma *et al.*, discussed the molecular mechanisms of the neuroprotective effects of resveratrol, and investigated the therapeutic potential in resveratrol as a therapeutic agent for Alzheimer's Disease[124].

3.2.2. Huntington's Disease(HD)

HD is an autosomal-dominant neurological disorder; the most striking pathological manifestation of the disease is a gradual loss of neurons predominantly in the striatum causing motor abnormalities and cognitive decline [125].In 2012,P.Kumar *et al.*, demonstrated that resveratrol plays significant role in Huntington's Disease .It shows beneficial effects against 3-nitropropionic acid suggest a role of the drug in protecting by neurotoxins in HD because 3-nitropropionic acid is an inhibitor of complex II of the electron transport chain, which causes HD's like symptoms. Resveratrol inhibits cyclooxygenase I (COX) activity significantly improving motor and cognitive impairments in the 3-nitropropionic acid-induced model of HD. [126].A. Granzotto *et al*., in 2011 and V. Desquiret-Dumas *et al*., in 2013 has observed that, resveratrol can effectively interject in the mitochondrial oxidation through its antioxidant properties and counteract impaired mitochondrial function through the activation of the SIRT1-PGC1α pathway [127,128].

In 2015,Ester Tellone *et al*., reviewed resveratrol and several neurodegenerative diseases and evaluated (in vivo and in vitro) the various molecular targets of resveratrol and its ability to effectively counter several neurodegenerative disorders such as Parkinson's, Alzheimer's, and Huntington's diseases and amyotrophic lateral sclerosis. It was found that, resveratrol through a convergence on the protein targets is able to give therapeutic responses in neuronal cells deeply diversified not only in morphological structure but especially in their function performed in the anatomical district to which they belong. [129]

3.2.3. Parkinson's disease (PD)

PD is the second most common neurodegenerative disorder after AD, affecting nearly 2% of individuals over the age of 65 in industrialized countries. [130].

Mitochondrial dysfunction, inflammation, oxidative stress and apoptosis appear to have a major role in the development and progression of PD. Different studies showed that resveratrol has neuro- protective function against the deleterious effect of 6-hydroxydopamine (6-OHDA) in rat models of PD. The conducted trials revealed that resveratrol suppresses the expression of pro-inflammatory cytokines (TNF-α) and enzymes (COX-2), which play a key role in the inflammatory process that is related with the progression of neurodegenerative diseases.In 2008, Jin *et al*.,demonstrated that the overexpression of COX-2 and TNF-α mRNA is

involved in the pathogenesis of PD and resveratrol can be used to reduce the levels of these proteins, resulting in improvement of pathological lesions in substantia nigra neurons in rat models of PD. These results confirm the beneficial effect of resveratrol in the treatment of PD. [131].

3.3. Cardio Protective Activity

The occurrence of the French paradox boosted the researchers to analyze the effect of resveratrol on people with a known predisposition to cardiovascular heart disease.Various studies has suggested that the resveratrol in red wine may play an important role in this phenomenon.The protective mechanism of resveratrol is due to its activity as intracellular antioxidant, anti-inflammatory agent, and due to its ability to induce angiogenesis and expression of nitric oxide synthase (Bhat *et al*., 2001) as well to block low-density lipoprotein (LDL) peroxidation and increase the levels of high-density lipoprotein (HDL) [132].

In 2010,Satyanand Tyagi *et al.,* stated that resveratrol plays important role in Inhibition of vascular cell adhesion molecule expression; Inhibition of vascular smooth muscle cell proliferation; Stimulation of endolethelial nitric oxide synthase (eNOS) Activity and inhibition of platelet aggregation.[133]. In the study conducted by Klinge *et al*., have analyzed the signaling pathways and molecular mechanisms by which resveratrol in concentrations compatible with oral consumption (nanomolar concentrations) is activating the protection against coronary heart diseases and is improving the function of endothelium of blood vessels [134]. It is found that nanomolar concentration of resveratrol is enough to stimulate rapidly nitric oxide production in endothelial cells by increasing the interaction between estrogen receptor α-Src and calveolin-1, which is one of the components of signaling pathway of resveratrol's protective action. As far as inflammation plays a key role in atherosclerosis, resveratrol can attenuate the condition through its anti-inflammatory effect, which involves inhibition of the synthesis of pro-inflammatory compounds such as prostaglandin E2 and interleukin-6 .[132].In 2017, Pollen K Yeungalso describes the therapeutic potential of resveratrol for cardiovascular protection. [204].

3.4. Anti –Diabetic Activity

In 2006,Su, H.-C. *et al*carried out an experiment of insulin like effect of resveratrol possesses in streptozotocin-induced diabetic rats. In which they evaluated its therapeutic potential by assaying the activities of key enzymes of carbohydrate metabolism in streptozotocin-nicotinamide-induced diabetic rats. The results demonstrated that the daily oral treatment of resveratrol (5 mg/kg body weight) to diabetic rats for 30 days showed a significant ($p<0.05$) decline in blood glucose and glycosylated hemoglobin levels and a significant ($p<0.05$) increase in plasma insulin level. The altered activities of the key enzymes of carbohydrate metabolism such as hexokinase, pyruvate kinase, lactate dehydrogenase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucose-6-phosphate dehydrogenase, glycogen synthase and glycogen phosphorylase in liver and kidney tissues of diabetic rats were significantly ($p<0.05$) reverted to near normal levels by the administration of resveratrol. Further, resveratrol administration to diabetic rats improved hepatic glycogen content suggesting the anti-hyperglycemic potential of resveratrol in diabetic rats. The obtained results were compared with glyclazide, a standard oral hypoglycemic drug. Thus, the modulatory effects of resveratrol on attenuating these enzymes activities afford a promise for widespread use for treatment of diabetes in the future. . [116].Other diabetic animal model studies by different researchers have also demonstrated the anti-diabetic effects of resveratrol. In human clinical trials, resveratrol has lowered blood sugar levels in both Phase Ib and Phase IIa, [135].

In 2017, K. Szkudelska *et al*., published a study regardinginfluence of resveratrol on some hormones and metabolic parameters in the rats ingesting 10% ethanol solution and concluded that resveratrol was found todiminish liver lipid accumulation and significantlyalleviated changes

in blood insulin and glucagon levelsexerting the protective action on the liver and endocrine pancreas[136].

3.5.Antioxidant Activity

Various compounds with aromatic groups are able to function as antioxidants by forming stable radicals via resonance structures, thereby preventing continued oxidation. Resveratrol contains two aromatic groups and has been shown to have a higher 2,2- azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), 1,1-diphenyl-2-picrylhydrazyl (DPPH), and hydroxyl radical scavenging
capacity than propyl gallate, vitamin C, and vitamin E [137].Resveratrol has been shown to inhibit oxidative-induced apoptosis in a variety of cell lines including Swiss 3T3 mouse fibroblasts, rat pheochromocytoma (PC12), human peripheralblood mononuclear (PBM), and human retinal pigment epithelium (RPE) cells. Reduced oxidative stress in RPE cells by resveratrol may be associated with reduced incidence of age-related macular degeneration (AMD), a leading cause of blindness in the elderly. [138,139,140].

Several evidences showed that resveratrol acts both as a free radical scavenger and a potent antioxidant, owing to its ability to promote the activity of numerous antioxidative enzymes. It is thought that resveratrol protects low-density lipoproteins (LDL) against peroxidation, leading to a regulated catabolism of LDL particles and thus avoiding atherosclerosis .Resveratrol also protects cellular and subcellular components, protecting cell membranes and preventing the effects of oxidative stress, leading to a reduction in cell death [21].Although resveratrol has been shown to exert antioxidant effects, it is not yet clear ifthis is primarily a direct scavenging effect or the result of the activation of pathways that upregulate cells' natural antioxidant defenses.

3.6.Anti-Aging (Life extension)Activity

Resveratrol can activate some specific genes linked to aging, such as PGC-1a, UCP2, in histone deacetylation, and the ratio NAD+ / NADH, evincing a positive effect on the biogenesis of mitochondria. Researchers state that resveratrol enhances the synthesis of ATP improving muscle performance, synthesis of insulin by the islets of Langerhan and reduction of inflammatory processes, that is to say, all affecting the elderly. [141].Some scientific evidence seems to indicate that resveratrol is a potent nutraceutical to prevent disease and delay aging. The vast majority of studies showed that resveratrol is an activator of sirtuins. Studies have established the action of resveratrol in processes such as activation of genes related to mitochondrial biogenesis, reduction of free radicals, ratio NAD+ / NADH in mitochondrial protein deacetylation, in modulating the ATP and others. Almost all authors who work with sirtuins and aging state that the molecular mechanism of how sirtuins retard aging and enhance life extension is not yet clear. [142].

It has been hypothesized that the main function of sirtuin proteins might be to promote survival and stress resistance in times of adversity.[143].An evolutionary advantage arising from the ability to modify lifespan in response to environmental conditions could have allowed these enzymes to be conserved as species evolved, and to take on new functions in response to new stresses and demands on the organism. This could explain why the same family of enzymes has dramatic effects on lifespan indisparate organisms with seemingly dissimilar causes of ageing.[144]..An in vitro screen for activators of SIRT1 identified resveratrol as the most potent of 18 inducers of deacetylase activity .Subsequent work has shown that resveratrol extends the lifespans of S. cerevisiae, Caenorhabditis elegans and Drosophila melanogaster ,but only if the gene that encodes SIR2 is present in these organisms[145,146].The first positive result was shown by vertebrate in 2006,when they were supplemented with resveratrol.An experiment with short-lived fish, *Nothobranchius furzeri* with the median life span of nine weeks showed not only 56% increase in median lifespan due to maximal dose of resveratrol but also showed significantly higher

general swimming activity and better learning to avoid the unpleasant stimulus and slight increase of mortality in young fishes. [99].

Resveratrol also consistently extends the mean and maximum life span in the model organisms including nematode worms. It has been suggested that resveratrol exerts its life-span-extending effect through calorie restriction or hormesis mimetic effects. This study showed that resveratrol increased mean and maximum life span by delaying the onset of the exponential increase in mortality characterizing the "dying phase" in C. elegans, but did not affect the dying phase itself, suggesting that it did not act by directly affecting metabolism.

[147].Afterwards some data suggested that resveratrol does not extend lifespan in healthy mice or in a model of premature aging [148]. but does appear to delay or attenuate many agerelated changes and prevent early mortality in obese animals [149,150].In 2017.Jessica Stockinger *et al*.,discovered that resveratrol increases the number of postsynaptic sites on myotubes exhibiting a youthful architecture and suggests that resveratrol directly affects the neuromuscular junctions. Also they have provided the compelling evidence indicating that resveratrol slows aging of neuromuscular junctions and muscle fibers.[151].

3.7. Anti-Inflammatory Activity

The anti-inflammatory effects of resveratrol have been demonstrated in several animal model studies. In a rat model of carrageenan-induced paw edema, resveratrol inhibited both acute and chronic phases of the inflammatory process. [152]. Similarly, preincubation with resveratrol decreased arachidonic acid release and COX-2 induction in mouse peritoneal macrophages stimulated with tumor promoter PMA, ROI, or lipopolysaccharides (LPS).[104].

In an experimental rabbit inflammatory arthritis model, resveratrol showed promise as a potential therapy for arthritis. When administered to rabbits with induced inflammatory arthritis, resveratrol protected cartilage against the progression of inflammatory arthritis.[153]. During inflammatory response, resveratrol elicits inhibitory effects in all physio pathological phases, suggesting that resveratrol could be effective in pharmacotherapy. In combination with its antioxidant properties, resveratrol also intervenes on enzyme systems involved in the synthesis of pro-inflammatory mediators, decreasing reactive oxygen species (ROS), which contributes to gastric ulcer healing and the reduction of colon injury.[154].

In 2017, Guangxi Wang *et al*.,reported that resveratrol had potent analgesic and anti-inflammatory activities and could be a potential new drug candidate for the treatment of inflammation and pain. [155].

3.8.Antimicrobial Activity

Increased resistance power of microorganisms against the several antibiotics is an emerging problem which has created the need of the agent showing the potential antimicrobial activity.Antibacterial therapy is a keystone of modern medicinal practice. However, the increased resistance of micro organisms to the currently used antimicrobials has lead to the evaluation of other agents with potential antimicrobialactivity. [156][157].Adaptation of microorganisms own defenses against the antibiotics used has made the development, proliferation and persistence of antimicrobial resistance, a currently major public health problem, making urgent the discovery of new drugs endowed with antimicrobial activity [158,159].

Nowadays, there is high demand of antimicrobial compounds obtained from natural sources .Thus, resveratrol, in addition to its therapeutic potentials has been the subject of study for its ability to inhibit the growth of some pathogenic microorganisms such as Gram-positive and Gram-negative bacteria and fungi [160] [161].In 2011, Paulo*et al.* reviewed the antimicrobial properties of resveratrol towards pathogenic microorganisms and also carried out investigation of the antibacterial properties of resveratrol against different Helicobacter pylori strains alongwith the analysis of

differentvirulence profiles and different susceptibility patterns against the antibiotics which are usually used in anti-H. pylori therapy.They had also verified the ability of resveratrol to inhibit activity of the H. pylori urease, the key enzyme in colonization and persistence of this pathogen.[29]

Resveratrol has shown the ability to inhibit the growth of some human pathogenic bacteria, such as *Klebsiella pneumonia, Helicobacter pylori, Listeria monocytogens* and *Staphylococcus aureus*. It has also able to show the antimicrobial activity against fungi, such as *Candida albicans,Trichosporon beigeli*[28].*Epidermophyton floccosum*. [162] and *Botrytis cinerea*, a common grapevine pathogen, slowing down or inhibiting the spread of this fungal infection [163].In 2010, Michela Campagna and Carmen Rivassummarized the knowledge of the activity of resveratrol against viral infection and describes the possible molecular pathways through which resveratrol exerts its antiviral activity. They found that resveratrol has been shown to be a potent antiviral molecule against various types of DNA and RNA viruses. However, even if the antiviral activity of resveratrol is becoming evident, the cellular pathways that lead to its protective activity are still far from being elucidated. [164].In 1997, Gehm BD *et al.*, found that during the cell culture study , resveratrol blocks the influenza virus from transporting viral proteins to the viral assembly site, hence restricting its ability to replicate. The effect was 90% when resveratrol was added six hours after infection and continued for 24 hours thereafter,itis demonstrated that resveratrol inhibits herpes simplex virus (HSV) types 1 and 2 replication by inhibition of an early step in the virus replication cycle. In vivo studies in mice found resveratrol inhibits or reduces HSV replication in the vagina and limits extravaginal disease. The skin of resveratrol-treated animals showed no apparent dermal toxicity, such as erythema, scaling, crusting, lichenification, or excoriation. [165] [166,167].Other Study showed that resveratrol inhibits varicella-zoster virus, certain influenza viruses, respiratory viruses, and human cytomegalovirus. Furthermore, resveratrol synergistically enhances the anti-HIV1 activity of several anti-HIV drugs[168,169].It isalso reported that the antibacterial activity of pterostilbene, a structural analog of resveratrol, in combination with gentamicin against six strains of Gram-positive and Gram-negative bacteria combinations could have effective therapeutic value against bacterial infections and these findings have potential implications in delaying the development of bacterial resistance as the antibacterial effect was achieved with the lower concentrations of antibacterial agents[170].

(Table.2. ICs of Resveratrol against bacteria and *C.albicans*) [171]

Microorganism	IC_{50} (mg/L)[a]	IC_{80}(mg/L)[b]
N. gonorrhoeae	25	75
N. *meningitidis*	100	125
E.coli	>200	>200
S.aureus	>200	>200
S.pyogenes	>200	>200
P.aeruginosa	>200	>200
C.albicans	>200	>200

It is experimentally proved that, the Resveratrol acts against bacteria and fungi. The bacteria includes the potent pathogens like *Neisseria gonorrhoeae* and *Neisseria meningititidis*. The mechanism by which Resveratrol inhibits these pathogens is unknown but it is reported to have a variety of physiological effects including antioxidant properties. The lack of activity against *E.coli, S.aureus,S.pyogenes,P.aeruginosa* is inconsistent with the studies carried out by many scientists,who found that Resveratrol had no effect on these microorganisms at low concentration at concentration less than 200 mg/L. on basis of this, it can beconcluded that the inhibitory concentrations i.e.IC_{50} and IC_{80} are found to be effective against abovementioned microorganisms.[171,172].Table.2.

4.0.LIMITATIONS TO HUMAN CLINICAL TRIALS

In 2013,Joao Tome-Carneiro *et al* reviewed the currently available evidence regarding resveratrol's effects on humans obtained from randomized clinical trials.It was found that

although, vast majority of preclinical studies have been performed using assay conditions with a questionable extrapolation to humans, i.e. too high concentrations with potential safety concerns (adverse effects and drug interactions), short-term exposures, in vitro tests carried out with non-physiological metabolites and/or concentrations, etc. [173].

Unfortunately, all these hypothesis-generating studies have contributed to increased the number of 'potential' benefits and mechanisms of resveratrol but confirmation in humans is very limited. Therefore, there are many issues that should be addressed to avoid an apparent endless loop in resveratrol research. The so-called 'Resveratrol Paradox', i.e., low bioavailability but high bioactivity, is a conundrum not yet solved in which the final responsible actor (if any) for the exerted effects has not yet been unequivocally identified.[174].Resveratrol represents a relatively new class of chemo preventive agent in comparison with retinoid and other diet-derived compounds. Although, it has proved to be capable of retarding or preventing steps of carcinogenesis in various in vitro and in vivo models, it is rather surprising that very little studies have assessed the effectiveness of resveratrol in humans. In part, this may be attributable to the pharmaceutical industry's reluctance to promote resveratrol, or any natural compound, in combating chronic diseases which may be otherwise targeted through more profitable proprietary drugs. [100].

4.1.Bioavailability and Pharmacokinetics of Resveratrol

Resveratrol has emerged as a leading candidate for improving health span as it able to slow down the aging process as well as prevents the chronic diseases. The limited bioavailability of resveratrol in humans has been a major concern for translating basic science findings into clinical efficacy. The bioavailability and metabolism of *trans*-resveratrol have been widely studied in rats and humans given that its efficacy depends on its absorption and metabolism [175]. However, it is difficult to provide an adequate pharmacokinetic description of the intricate processes that determine the bioavailability of resveratrol. A preliminary evaluation of the plasmatic pharmacokinetics of *trans*-resveratrol was carried out after the oral administration of 2 mg/kg to overnight fasted rats .Blood samples were extracted at different time points over an hour, and showed low plasmatic concentrations of unchanged *trans*-resveratrol with peak concentration of 550 ng/mL at 10 minutes. [177]. The low bioavailability for *trans*-resveratrol indicates that the small intestine comes out as the first bottleneck to the entry of this compound to the organism.[176,178]

The pharmacokinetics of resveratrol shows two interesting characteristics worth consideration, however, these require further study for corroboration. Firstly, the administration of Resveratrol is circadian dependent, as the AUC (Area Under the Curve) in a plasma level graph is larger after morning than after afternoon oral administration [179,180].Consequently, bioavailability of resveratrol would be higher if administered in the morning. Secondly, as mentioned, the pharmacokinetic parameters have high interindividual variability, with variance coefficients of around 40%, in which the impact of patient gender or age is insignificant, as shown in comparisons of groups of men and women, young and older people [181].

In 2013, Sharan and Nagar showed that the body extensively metabolized resveratrol where gut,liver and lungs are the mainly positions of resveratrol metabolism.[182] .In 2005, Wenzel and Somoza reported that around 75% of resveratrol is removed by urine and excreta .Very limited information is available on the excretion of resveratrol [183]. Boocock DJ *et al*(2007) and Brown V.A,*et al* (2010) demonstrated that total clearance of resveratrol ranges between 2.5 to 3.0 l/h (41.7 ml/min to 50 ml/min).[184,185].The elimination half-life (t½) has been calculated at 1.1 h after a dose of 100 mg Resveratrol , while after 1.0 g/ day administration for 21 days, the t½ is 9.7 h [179,180].Resveratrol is eliminated relatively quickly and it has been reported that up

to 77% of the dose is eliminated within the first four hours post-administration.[186].In 2013,Augustin *et al.*, reported that bioavailability of resveratrol is low or zero for almost time and may be attributed to speed and extensive metabolism or its limited water solubility and the consequent compound of different metabolites such as resveratrol sulphates and resveratrol glucuronides.[187].

Absorption of resveratrol is affected due to its low water solubility (0.03 g/L) .In order to increase its solubility, ethanol (50g/L) or organic solvents may be used. It is important to highlight the ability of resveratrol to form a wide range of organic molecular complexes. Sterification of hydroxyl groups with aliphatic molecules can also be employed as a tool to increase its intestinal absorption and cellular permeability. For example, resveratrol acetylation can increase its absorption and its cellular capture without loss of activity [188,189].

In 2011, D. Delmas *et al*studied the absorption level of resveratrol at intestinal level and found that resveratrol is absorbed by passive diffusion or forming complexes with membrane transporters, such as integrins. Once in the bloodstream, resveratrol can be found essentially in three different forms: glucuronide, sulfate, or free. The free form can be bound to albumin and lipoproteins such as LDL (low-density lipoprotein). These complexes, in turn, can be dissociated at cellular membranes that have receptors for albumin and LDL, leaving the resveratrol free and allowing it to enter cells. [205].Resveratrol's affinity for albumin suggests that it could be a natural polyphenolic reservoir, playing an important role in its distribution and bioavailability M. Urpı-Sarda *et al* has stated that , resveratrol can interact with fatty acids due to its chemical characteristics and the *in vitro* studies showed that more than 90% of free *trans*-resveratrol binds to human plasma lipoproteins.This binding is also found *in vivo*, as shown by the presence of dietary polyphenolic compounds detected in isolated LDL in blood samples of healthy human volunteers[190] .[191]

There is surprisingly very little data regarding the bioavailability of resveratrol in humans.If bioavailability is indeed a limitation in the clinical utility of resveratrol, there is a need to further explore methods to optimize bioavailability in humans. [191].Encapsulated resveratrol provides a potential approach for improving the solubility of resveratrol, consequently enhancing it's bioavailability. [187].In 2016, Balata G *et al*., demonstrated the potential usefulness of self-emulsifying drug delivery systems in the improvement of dissolution rate and thereby oral bioavailability of resveratrol compared to unprocessed drug [192].

5.0. Nano-technological Solution Over Limited Bioavailability

Now-a-days research community has been trying to find techniques to enhance bioavailability of resveratrol and recently there are number of studies which are related to use of nanotechnology to improve the bioavailability of resveratrol. There is emerging evidence that nano formulations of resveratrol can protect resveratrol from metabolism during the digestive process, which ultimately increases tissue absorption in animal models [193]. Nano formulations can improve resveratrol's solubility and transport across the plasma membrane, and thus enhance its effects within cells. [194] .In 2010,Frozza, R.L *et al*reported that resveratrol loaded onto lipid-core nanocapsules improved tissue concentration in the brain, liver, and kidney of healthy rats compared to free resveratrol .Additionally, the nanocapsule formulation decreased gastrointestinal damage in rats which suggests such a formulation could improve tolerability in humans while also increasing bioavailability.[195].In 2010, Guo, L *et al.,* stated that in the model of ovarian cancer, resveratrol-bovine serum albumin nanoparticles initially demonstrated greater blood concentration than resveratrol alone following intraperitoneal injection. However, the nanoparticle formulation achieved greater tissue distribution to the liver, heart, kidney, and ovary, and ultimately it was

found to be more efficientthan standard resveratrol. Similarly, resveratrol loaded solid nanoparticles proved selectively greater distribution to the brain, yet similar or even lower distribution to other tissues compared to free resveratrol .[196,197].

Comprehensive reviews of nanotechnological approaches to increase the bioavailability of resveratrol and other phytochemicals have recently been published. [198,199].Though nanotechnology holds much promise for enhancing the bioavailability of resveratrol, considerable work must be done in this realm, which may be specific to intended use (e.g., general cardiovascular *vs*. cancer chemotherapeutic) and route of delivery (e.g., dermal *vs.* oral *vs*. intravenous). Nonetheless, these nano-technological approaches are yet to be attempted in humans. [191].

In 2015, Imtiaz A. Siddiqui*et al.*, demonstrated recent novel nano technological approaches used to deliver sustained levels of resveratrol .It was observed that to date, no resveratrol-based nanosystems have been approved for clinical use, and this would provide the driving force for further evolution of research on innovative nanodevices able to consolidate the chemopreventive potential of resveratrol. [200]

6.0. CONCLUSION

In modern lifestyle, society is desperately concern about nutritional food derived from natural resources. In this perspective, nutraceuticals has been proved to be the foundation of several research studies throughout the world. Recent lifestyle as well as environmental pollution leads to number of diseases and disorders. Accordingly, desire of consumers, for plant-derived products with potent biological properties has been increased. Resveratrol is clinically proved to be the remedy for various disorders and there is high demand for large scale production of resveratrol due to its application in nutraceutics cosmetics and pharmaceutics etc. This review summarizes the natural biosynthesis of resveratrol with respect to grapevine as well as the brief knowledge on the biosynthetic pathway of resveratrol has been stated. Significance of grapevine plant for natural production of resveratrol by means of various biotic and abiotic elicitors in order to achieve the maximum induction and/or elicitation of resveratrol in grapevine and its cell suspension cultures is also systematically included in it.

This review focuses on ability of some fungal pathogensviz.*Botrytis cinerea,Plasmopara viticola,Rhizopus stolonifer,Uncinula necator* , few bacterial strain(genus Bacillus) and some chemicals to elicit resveratrol production of.The studies on antibacterial activity of resveratrol indicated that the potent pathogens *like N.meningitidis and N.gonorrhoae* are inhibited whereas other normal flora such as *E.coli, S.aureus,S.pyogenes,P.aeruginos* are not inhibited at low concentration. The inhibition of potent pathogens seems to be important to overcome the related disorders whereas,the opportunistic pathogens are not inhibitedgiving a great advantage to resveratrol as a neutral agent in the human therapy.

This review also presents the clinical potential of resveratrol in the prevention and treatment of various diseases and disorders like cancer, cardiovascular diseases, neurodegenerative disorders, diabetes and chronic respiratory diseases etc and .highlighted the limitations of bioavailability of resveratrol and pharmacokinetics along with possible solutions with regard to nanotechnology.

7.0. FURTHER RECOMMENDATIONS

Although, resveratrol is very remarkable compound due to its diverse potential and biological activities, its bioavailability limits the clinical applications of resveratrol.Therefore, continued efforts towards optimizing the bioavailability of resveratrol and determining its pharmacokinetics, pharmacodynamics and safety profile in different populations consisting, all the age groups including the pregnant women are needed.

In view of the high demand for resveratrol, further research should be carried out for

enhanced resveratrol production from cell suspension culture. As well as there is necessity for finding out the efficient elicitors which can increase the resveratrol level in indigenous as well as worldwide grapevine cultivars.

Further study for development of best operating conditions for achievement of high amount of trans-resveratrol in the grapevine cell suspension culture in harmony with biotic and abiotic elicitors for nutraceutical applications is required.

There is need to explore the intellectual property right concerning the Indian traditional knowledge and ancient medicinal practices with respect to *Ayurvedic* rejuvenating and healing formulations by use of grapes and grape products.

ACKNOWLEDGEMENT

Authors would like to acknowledge Prin. V. N. Suryavanshi and Department of Microbiology, H.P.T .Arts and R.Y.K. Science College, Nashik, India for cordial support. Authors are highly thankful to Mr.D.V.Handore,Research Mentor,Sigma Winery Pvt. Ltd.Nashik for valuable scientific inputs.

REFERENCES

1. Donnez D., Jeandet, P., Clémont C., Courot E., (2009), Bioproduction of resveratrol and stilbene derivatives by plant cells and microorganisms, Trends Biotechnol Vol..27, pp.706-713.
2. George J.Soleas,Eleftherios P.Diamandis and David M.Goldberge ., (1997), 'Resveratrol :A Molecule Whose Time Has Come? and Gone ?Clinical Biochemistry,Vol.30,(2). pp91-113,
3. Murcia M.A.and M.Martinez-Tome.,(2001).Antioxidant activity of resveratrol compared with common food additives, J.Food Prot., Vol..64,pp.379-384
4. Prokop,J.,P.Abrman,A.L.Seligson and M.Sovak.,(2006),Resveratrol and its glycon piceid are stable polyphenols, J.Med.Food, Vol..9,pp.11-14
5. Mishra R.N..,(2011),Resveratrol,The new rasayan(Anti-aging) drug, Current Research in Medicine and Medical Sciences Vol.1(1).pp.5-18.
6. Sales JM, Resurrección, A. V.,(2013), A. Resveratrol in Peanuts. Crit Rev Food Sci in press
7. Pervaiz,s.,(2003,).Resveratrol :from grapevines to mammalian biology FASEB Journal,Vol.17.(. 14).,pp.1975-1985
8. Trela B, Waterhouse, A. L. Resveratrol: isomeric molar absorptivities and stability., (1996),J Agr Food Chem Vol.44,pg.1253-1257.
9. Jeandet P., Hebrard C., Deville M.A., Cordelier S., Dorey S., Aziz A. and Crouzet, J., (2014),.Deciphering the role of ph,(ytoalexins in plant-microorganism interactions and human health. Molecules , Vol.19: pp.18033–18056
10. Yang, M.H.; Kuo, C.H.; Hsieh,W.C.; Ku, K.L.2010),Investigation of microbial elicitation of trans-resveratrol and trans-piceatannol in peanut callus led to the application of chitin as a potential elicitor. J. Agric. Food Chem., Vol.58.pp.9537–9541
11. Suzuki, M.; Nakabayashi, R.; Ogata, Y.; Sakurai, N.; Tokimatsu, T.; Goto, S.; Suzuki, M.; Jasinski, M.; Martinoia, E.; Otagaki, S.,(2015). Multiomics in grape berry skin revealed specific induction of the stilbene synthetic pathway by ultraviolet-c irradiation. Plant Physiol., Vol.168.pp.47–59
12. Hain R., Reif H.J., Krause E., Langebartels R., Kindl H., Vernau B., Weise W., Schmatzer, E.and Schreier, P.H.,(1993), Disease resistance results from foreign phytoalexin expression in a novel plant. Nature, Vol. 361.pp.153–156.
13. Wiese W., Vornam B., Krause E. and Kindl H,.(1994)., Structural organization and differential expression of three stilbene synthase genes located on a 13 kb grapevine DNA fragment. Plant Molec. Biol., Vol..26.pp.667-677.
14. Dercks, W. and Creasy L.L.(1989).The significance of stilbene phytoalexins in the plasmora viticola-grapevine interaction. Physiol. Mol. Plant Pathol., Vol.34.pp.189–202
15. Langcake P. and Pryce R.J.,(1976) ,The production of resveratrol by *Vitis vinifera* and other members of the vitaceae as a response to infection or injury. Physiol. Plant Pathol, Vol.9.pp 77–86.

16. Ingham J. L.,(1976), 3,5,4′-Trihydroxystilbene as a phytoalexin from groundnuts (Arachis hypogaea). Phytochemistry,Vol.15,pp.1791–1793
17. Kuc, J.,(1995)Phytoalexins, stress metabolism, and disease resisteance in plants. Ann. Rev. Phytopathol, Vol.33,pp.275–297
18. Halls C. and Yu O.,(2008). Potential for metabolic engineering of resveratrol biosynthesis. Trends Biotechnol. , Vol.26,(.2),.pp.77-81
19. Quideau S, Deffieux, D., Douat-Casassus, C., Pouységu, L.,(2011),.Plant polyphenols: chemical properties, biological activities, and synthesis. Angew Chem Int Edit, Vol..50. pp.586-621
20. Van Wyk BE, Gericke, N. (,2000),.People's plants: a guide to useful plants of Southern Africa. South Africa: Briza Publications:,Vol.11.
21. Jeandet P., Delaunois B., Aziz A., Donnez D., Vasserot Y., Cordelier S., Courot E., (2012).,Metabolic enginnering of yeast and plants for the production of the biologically active hydroxystilbene, resveratrol. J Biomed Biotechnol pp.1-14
22. Lim C.G., Fowler Z. L., Hueller T., Schaffer S. and Koffas M. A. G., (2011),.High-yield resveratrol production in engineered Escherichia coli. Appl Environ Microb, Vol..77. pp.3451-3460.
23. Hasan M. Mohidul and Hanhong Bae, (2017),An Overview of Stress-Induced Resveratrol Synthesisin Grapes: Perspectives for Resveratrol-Enriched Grape Products, Molecules, Vol.. 22 pp.294
24. Cucciolla V., Borriello A., Oliva A., Galletti P., Zappia V. and Ragione, F. D., (2007).,Resveratrol – from basic science to the clinic. Cell Cycle, Vol..6. pp.:2495-2510
25. Burns J, Yokota, T., Ashihara, H., Lean, M. E. J., Crozier, A.,(2002), Plant foods and herbal sources of resveratrol. J Agr Food Chem; Vol..50 pp. 3337-3340
26. Takaoka, M. J. (1940).The phenolic substances of white hellebore (Veratrum grandiflorum Loes. fil.). J. Faculty Sci. Hokkaido Imperial University pp.3:1–16
27. Shin S-Y, Han, N. S., Park, Y-C., Kim, M-D. Seo, J-H, (2010),,Production of resveratrol from p-coumaric acid in recombinant Saccharomyces cerevisiae expressing 4-coumarate:coenzyme A ligase and stilbene synthase genes. Enzyme Microb Tech .Vol..48 pp.:48-53
28. Sultanbawa Y.,(2011), Plant antimicrobials in food applications: minireview. In: A. Méndez-Vilas editor. Science against microbial pathogens: communicating current research and technological advances: Formatex: pp.1084-1093
29. Paulo L, Domingues, F., Queiroz, J. A., Gallardo, E.,(2011), Development and validation of an analytical method for the determination of trans- and cis-resveratrol in wine: analysis of its contents in 186 portuguese red wines. J Agr Food Chem Vol..59pp.2157-2168
30. Goldberg, D. M., (1995),.A global survey of trans-resveratrol concentrations in commercial wines. Am. J.Enol. Vitic., Vol..46 pp.159–165
31. Langcake P. and Pryce R.J.,(1977),The production of resveratrol and the viniferins by grapevines in response to ultraviolet irradiation. Phytochem, Vol..16 pp.1193-1196.
32. Creasy L. and Coffee M..,(1988),Phytoalexin production potential of grape berries. J. Amer.Soc. Hort. Sci., Vol.. 113 pp.:230-234.
33. Jeandet P., Bessis R. and Gautheron B.(1991),The production of resveratrol by grape berriesin different developmental stages. Amer. J. Enol. Viticult. , Vol.. 42 pp.41-46.
34. Richter, H., Pezet, R., Viret, O. and Gindro, K,(2006),Characterization of 3 new partial stilbene synthase genes out of over 20 expressed in *Vitis vinifera* during the interaction with Plasmopara viticola. Physiol. Mol. Plant. Path. Vol.. 67 pp. 248-260.
35. Velasco, R., Zharkikh, A., Troggio, M., Cartwright, D.A., Cestaro, A,.(2007).A high quality draft consensus sequence of the genome of a heterozygous grapevine variety. PLoS OneVol.2(12) pp.1326.-1371
36. Romero-Perez, A. I., Lamuela-Raventos, R. M., Andres-Lacueva, C. & de La Torre-Boronat, M. C.,(2001).Method for the quantitative

extraction of resveratrol and piceid isomers in grape berry skins. Effect of powdery mildew on the stilbene content. J. Agric. Food Chem. Vol..49, pp. 210–215

37. J. Lachman, M. Šulc, A. Hejtmánková, V. Pivec, M. Orsák, (2004) ,Content Of Polyphenolic Antioxidants And Trans-Resveratrol In Grapes of Different Varieties Of Grapevine (*Vitis vinifera* L.)Hort. Sci. (Prague), Vol..31, (2) pp. 63–69
38. Ulrik Stervboa,b, Ole Vanga, Christine Bonnesen,,(2007),A review of the content of the putative chemopreventive phytoalexin resveratrol in red wine, Food Chemistry Vol..101,pp.449–457
39. Adrian M., Jeandet P., Douillet-Breuil A.C., Tesson L and Bessis R.,(2000),Stilbene content of mature *Vitis vinifera* berries in response to UV-C elicitation. Journal of Agricultural and Food Chemistry, Vol..48,pp.6103–6105.
40. Douillet-Breuil A.C., Jeandet P., Adrian M., and Bessis N.,(1999),Changes in phytoalexin content of various Vitis Spp.in response to ultraviolet C elicitation., Journal of Agricultural and Food Chemistry, Vol..47(10) .pp.4456-4461
41. Pastor RF, GargantiniMR,MurgoM, Prieto S,Manzano H, AruaniC, Quini CI, Covas MI.,(2015), Enrichment of resveratrol inwine through a new vinification procedure. J Life Sci Vol.9:327–333
42. Prajitna, A., Dami, I.E., Steiner, T.E., Ferree, D.C., Scheerens, J.C. and Schwartz, S.J. (2007), Influence of cluster thinning on phenolic composition, resveratrol, and antioxidant capacity in Chambourcin wine. Am. J. Enol. Vitic. Vol..58(3) pp. 346-350.
43. Berli F., D'Angelo J., Cavagnaro B., Bottini R., Wuilloud R. and Silva M.F.,(2008), Phenolic composition in grape (*Vitis vinifera* L. cv. Malbec) ripened with different solar UV-B radiation levels by capillary zone electrophoresis. J. Agric. Food Chem,Vol.56: 2892-2898
44. Bavaresco, L.; Pettegolli, D.; Cantu', E.; Fregoni, M.; Chiusa, G.; Trevisan, M.,(1997),Elicitation and accumulation of stilbene phytoalexins in grapevine berries infected by Botrytis cinerea. Vitis, Vol.36, 77–83.
45. Dugo, G.; Saitta, M.; Giuffrida, D.; Vilasi, F.; LA Torre, G.L. .,(2004), Determination of resveratrol and other phenolic compounds in experimental wines from grapes subjected to different pesticide treatments. Ital. J. Food Sci,Vol.3 pp.16–20.
46. R.T.Threlfall and J.R.Morris,1996,effect of viticultural and enological methods on resveratrol content of wines,Proceedings,4th International Symp Cool Clim Vitic and Enol.NY .pp.100
47. Kostadinović S, Wilkens A, Stefova M, Ivanova V, Vojnoski B, Mirhosseini H, Winterhalter P.,(2012), Stilbene levels and antioxidant activity of Vranec and Merlot wines from Macedonia: effect of variety and enological practices, Food Chem. Vol.15;135(4)
48. Sutton, J.C., and G. Peng ,(1993). Biocontrol of Botrytis cinerea in strawberry leaves. Phytopathology.Vol.83 pp.615-621
49. Paul Bernard, Alphonsa Chereyathmanjiyil , Isaac Masih , Laurence Chapuis ,Armelle Benot , (1998),Biological control of Botrytis cinerea causing grey mould disease of grapevine and elicitation of stilbene phytoalexin (resveratrol) by a soil bacterium, FEMS Microbiology Letters .Vol.165 pp.65-70
50. Delmas D., Lancon A., Colin D., Jannin B. and Latruffe N.,(2006),.Resveratrol as a Chemopreventive Agent: A Promising Molecule for Fighting Cancer. Current Drug Targets, Vol.7 pp.423–442
51. Liswidowati, Frauke Melchior, Frank Hohmann, Burkhardt Schwer and Helmut Kindl.(1991),.Induction of stilbene synthase by Botrytis cinerea in cultured grapevine cells,Planta, Vol.183 pp.307-314.
52. Montero, C.; Cristescu, S.M.; Jiménez, J.B.; Orea, J.M.; Lintel Hekkert, S.T.; Harren, F.J.M.; González Ure ´ n, (2003), A.Trans-resveratrol and grape disease resistance. A dynamical study by high-resolution laser-based techniques.Plant Physiol. Vol.131,pp.129–138.
53. Timperio, A.M.; D'Alessandro, A.; Fagioni, M.; Magro, P.; Zolla, L.,(2012,). Production of

the phytoalexins trans-resveratrol and delta-viniferin in two economy-relevant grape cultivars upon infection with Botrytis cinerea in field conditions. Plant Physiol. Biochem., Vol.50, pp.65–71.

54. Langcake, P. 1981, Disease resistance of Vitis spp. and the production of the stress metabolites resveratrol,"-viniferin,-viniferin, and pterostilbene. Physiol. Plant Pathol.,Vol..18, pp.213–226.
55. Sarig, P.; Zutkhi, Y.; Monjauze, A.; Lisker, N.; Ben-Arie, R..,(1997), Phytoalexin elicitation in grape berries and their susceptibility to Rhizopus stolonifer. Physiol. Mol. Plant Pathol., Vol..50, pp.337–347
56. Fornara V, Onelli E, Sparvoli F, Rossoni M, Aina R, Marino G,Citterio S ,(2008) ,Localization of stilbene in *Vitis vinifera* L.during berry development. Protoplasma .Vol..233: pp.83–93
57. Luis Alberto Madrigal-Perez and Minerva Ramos-Gomez.,(2016), Resveratrol Inhibition of Cellular Respiration:New Paradigm for an Old Mechanism, Int. J. Mol. Sci. Vol..17, pp.368
58. Fan E., Zhang K., Zhu M. and Wang Q.,(2010),Obtaining resveratrol: From chemical synthesis to biotechnological production,. Org. Chem, Vol.7 pp.272–281
59. Solladié, G.; Pasturel-Jacopé, Y.; Maignanb, J. A,. (2003)., re-investigation of resveratrol synthesis by perkins reaction. Application to the synthesis of aryl cinnamic acids. Tetrahedron Lett. Vol.59 .pp.3315-3321
60. Sinha, A. K., Kumar, V., Sharma, A., Kumar, R..(2007),An unusual, mild and convenient one-pot two-step access to (E)-stilbenes from hydroxyl-substituted benzaldehydes and phenylacetic acids under microwave activation: A new facet of the classical Perkin reaction. Tetrahedron Vol.63. pp.11070– 11077
61. Moreno-Manas,M., Pleixats,R., (1985),.Dehydroacetic acid chemistry. A new synthesis of resveratrol, a phytoalexin of *Vitis vinifera*. Anal. Quim., Vol..81 pp. 157–161.
62. Maryanoff, B. E., Reitz, A. B.,(1989),The Wittig olefination reaction and modifications involving phosphoryl-stabilizedcarbanions. Stereochemistry, mechanism and selected synthetic aspects. Chem. Rev.Vol. 89, pp.863–927
63. Rao RS, Ravishankar, G. A..,(2002),.Plant cell cultures: chemical factories of secondary metabolites. Biotechnology Adv; Vol.20, pp.101–153.
64. Moscatiello, R.; Baldan, B.; Navazio, L. Plant cell suspension cultures. Methods Mol. Biol.2013, Vol..953, pp.77–93.
65. Krisa S., Larronde F., Budzinski H., Descendit A.,(1999),.Stilbene production by *Vitis vinifera* cell suspension cultures: Methyljasmonate induction and 13C-biolabeling. J. Nat. Prod., Vol..62.pp.1688–1690.
66. Bru, R. and Pedreno, MA. .2003. Method for the production of resveratrol in cell cultures. PCT patent WO/2003/062406. US 2006/0205049 A1.
67. Bru, R., Sell´es, S., Casado-Vela, J., Belchi-Navarro, S,.(2006),Modified cyclodextrins are chemically defined glucan inducers of defense responses in grapevine cell cultures. J. Agric. Food Chem, Vol.54 pp.65–71
68. Aziz, A., Trotel-Aziz, P., Dhuicq, L., Jeandet, P.,(2006),Chitosan oligomers and copper sulfate induce grapevine defense reactions and resistance to fungal pathogens. Phytopathology, Vol..96 pp.1188–1194.
69. Yang, F, Zhang, T, Ito, Y.,(2001),.Large-scale separation of resveratrol, anthraglycoside A and anthraglycoside B from Polygonum cuspidatum Sieb et Zucc by high-speed counter-current chromatography. J. Chromatogr. A ,Vol.919 pp.443–448
70. Tassoni A., Fornalè S., Franceschetti M., Musiani F., Michael A., Perry B. and Bagni N.,(2005), Jasmonates and Na-orthovanadate promote resveratrol production in *Vitis vinifera* cv. Barbera cell cultures, New Phytologist ,Vol.166, pp.895–905
71. Belhadj A., Telef, N., Saigne C. and Cluzet S.,(2008), Effect of methyl jasmonate in combination with carbohydrates on gene expression of PR proteins, stilbene and anthocyanin accumulation in grapevine cell cultures. Plant Physiol. Biochem. ,Vol.46,pp.493–499

72. Donnez D., Kim K. H., Antoine S. and Conreux A.,(2011),.Bioproduction of resveratrol and viniferins by an elicited grapevine cell culture in a 2L stirred bioreactor. Process Biochem,Vol.46, pp.1056–1062.
73. M. Adrian , P. Jeandet , R. Bessis , and J. M. Joubert , Induction of Phytoalexin (Resveratrol) Synthesis in Grapevine Leaves Treated with Aluminum Chloride (AlCl3), J. Agric. Food Chem..,(1996), Vol..44 (8), pp 1979–1981
74. Jiménez J.B., Orea J.M., González Urena A., Escribano P., López de la Osa P., Guadarrama A.,(2007),Short anoxic treatment to enhance trans-resveratrol content in grapes and wine. European Food Research and Technology, Vol.224,pp. 373–378.
75. Zamboni, A., Gatto, P., Cestaro, A., Pilati, S.,(2009), Grapevine cell early activation of specific responses to DIMEB, a resveratrol elicitor. BMC Genomics Vol.10,pp.363.
76. Belchi-Navarro, S., Almagro, L., Sabater-Jara, A. B., Fernandez-Perez, F,.(2013),Early signaling events in grapevine cells elicited with cyclodextrins and methyljasmonate. Plant Physiol. Biochem.,Vol..62 pp.107–110.
77. Almagro L.,Belchi-Navarro S.,Sabater-Jara A.B and Vera-Urbina J. C.(2013),.Bioproduction of trans-resveratrol from grapevine cell cultures, in: Ramawat, K. G., Merillon, J. M. (Eds.), Handbook of Natural Products, Springer-Verlag, Berlin, Heidelberg, pp.1683–1713.
78. Lijavetzky D., Almagro L., Belchi-Navarro S. and Martinez- Zapater J. M.,(2008.),Synergistic effect of methyljasmonate and cyclodextrin on stilbene biosynthesis pathway gene expression and resveratrol prodution inMonastrell grapevine cell cultures. BMC Res. Notes ,Vol. 1,pp. 132
79. Belchi-Navarro, S., Almagro, L., Lijavetzky, D., Bru, R.(,2012), Enhanced extracellular production of trans-resvertrol in *Vitis vinifera* suspension cultured cells by using cyclodextrins and methyljasmonate. Plant Cell Rep. Vol..31,pp.81–89.
80. Hasan, M.M.; Baek, K.H..,(2013),Induction of resveratrol biosynthesis in grape skin and leaves by ultrasonication treatment. Korean J. Hortic. Sci. Technol.,Vol.31,pp. 496–502
81. Tobias Sydor, Steffen Schaffer, and Eckhard Boles.,(2010),Considerable Increase in Resveratrol Production by Recombinant Industrial Yeast Strains with Use of Rich Medium, Applied And Environmental Microbiology, pp. 3361–3363
82. C. Bejan, E. Visoiu,.,(2011) Resveratrol biosynthesis in vitro culture conditions on grapevine (cv. Feteasca neagra and Cabernet Sauvignon) under the action of AlCl3 as elicitor agent. In: Romanian Biotechnological Letters Vol. 16, No.6, pp.97-101.
83. Martinez-Esteso, M. J., Sell´es-Marchart, S., Vera-Urbina, J. C., Pedreno, M. A.,(2009),Changes of defense proteins in the extracellular proteome of grapevine (*Vitis vinifera* cv. Gamay) cell cultures in response to elicitors. J. Proteomics, Vol..73, pp.331–341.
84. Yue, X., Zhang, W., Deng, M., (2011),.Hyper-production of 13Clabelled trans-resveratrol in *Vitis vinifera* suspension cell culture by elicitation and in situ adsorption. Biochem. Eng. J.Vol.53.pp.292–296.
85. Morales,M., Bru, R., Garcia-Carmona, F., Ros Barcelo, A.,(1998)..Effect of dimethyl-β-cyclodextrins on resveratrol metabolism in Gamay grapevine cell cultures before and after inoculation with Xylophilus ampelinus. Plant Cell Tissue Organ Cult. Vol.53 pp.179–187.
86. Bru,M. R., Pedreno, G.M.,(2007),.Methods for the productionof resveratrol in cell cultures. US Patent 7309591
87. Cantos E., Espin J.C., Tomás-Barberán F.A.(2001),Postharvest induction modeling method using UV irradiation pulses for obtaining resveratrol-enriched table grapes: A new “Functional” fruit? ,Journal of Agricultural and Food Chemistry,.Vol.49 pp. 5052–5058.
88. Sbaghi,M.,Jeandet,P.,Faivre,B.,Bessis,R.etal..,(1995),Developmentof methods using phytoalexin (resveratrol) assessment as a selection criterion to screen grapevine in vitro cultures forresistance to grey mould (Botrytis cinerea) Euphytica ,Vol..86 pp.41–47
89. Sarig P., Zahavi T., Zutkhi Y., Yannai S., Lisker N., Ben-Arie R.,1996).,Ozone for control of post-harvest decay of table grapes

caused by Rhizopus stolonifer. Physiological and Molecular Plant Pathology, Vol..48,pp.403– 415.

90. Artés-Hernández F., Artés, F., Tomás-Barberán F.A.,(2003),Quality and enhancement of bioactive phenolics in cv. Napoleon table grapes exposed to different postharvest gaseous treatments. Journal of Agricultural and Food Chemistry, Vol.51,pp. 5290–5295.
91. González-Barrio R.,Beltrán D.,Cantos E.,Gil M..I., Espín J.C., Tomás-Barberán F.A.,(2006.),Comparison of ozone and UV-C treatments on the postharvest stilbenoid monomer, dimer, and trimer induction in var. 'Superior' white table grapes. Journal of Agricultural and Food Chemistry, Vol.54 ,pp.4222–4228 .
92. J.A. Cayuela, A. Vázquez, A.G. Pérez,J.M. García,.,(2009),Control of Table Grapes Postharvest Decay by Ozone Treatment and Resveratrol Induction, Food Science and Technology International, Vol 15, (5)
93. Global Action Plan For The Prevention and Control of Non communicable Diseases 2013-2020
94. Y. Yilmaz and R. T. Toledo.(2004),Health aspects of functional grape seed constituents," Trends in Food Science & Technology, Vol..15(9) pp. 422–433,
95. Vel Szic, K. S., Ndlovu, M. N., Haegeman, G., Vanden Berghe, W.,(2010),.Nature or nurture: let food be your epigenetic medicine in chronic inflammatory disorders. Biochem. Pharmacol,Vol.80, pp.:1816–1832
96. Beavers, K. M., Brinkley, T. E., Nicklas, B.J.,(2010.),Effect of exercise training on chronic inflammation. Clin. Chim. Acta .Vol.411 pp.785–793
97. Baur, J. A., Resveratrol, sirtuins, and the promise of a DR mimetic. Mech. Ageing Dev,(2010), Vol..131 pp.261–269.
98. Jang M, Cai L, Udeani G.O, Slowing K.V., Thomas C.F., Bleecher C.W.W., Fong H.H.S., Farnsworth N.R., Kinghorn A.D., Mehta R.G., Moon R.C., Pezzuto J.M.,(1997),Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Sci Vol..275(5297) pp.218–20.
99. Baur, J. A., K.J. Pearson, N.L. Price, (2006),Resveratrol improves health and survival of mice on a high-calorie diet. NatureVol.444 pp.337–342
100. Smoliga, J. M., Vang, O., Baur, J. A.,(2011), Challenges of translating basic research into therapeutics: resveratrol as an example. J. Gerontol. A Biol. Sci. Med. Sci. in press.
101. Dong H.S., Mi-Kyung K., Hee Seung K., Hyun H. C., and Yong S. S.,(2013), Cancer-specific Therapeutic Potential of Resveratrol: Metabolic Approach against Hallmarks of Cancer- Review Article, Functional Foods in Health and Disease , 3(8) pp.:332-343
102. Muqbil I, Beck FW, Bao B, Sarkar FH, Mohammad RM, Hadi SM, Azmi AS.(2012),.Old wine in a new bottle: the Warburg effect and anticancer mechanisms of resveratrol. Current pharmaceutical design Vol.18(12) pp.1645-1654
103. Clement M.V., Hirpara J.L., Chawdhury S.H. and Pervaiz S.,(1998).,Chemo preventive agent resveratrol, a natural product derived from grapes, triggers CD95 signaling-dependent apoptosis in human tumor cells. Blood , Vol.92(3) pp.92996–1002
104. Tsai SH, Lin-Shiau SY & Lin JK..,(1999),Suppression of nitric oxide synthase and the down-regulation of the activation of NFkB in macrophages by resveratrol. British Journal of Pharmacology,Vol.126: pp.673–680.
105. Jang M., Cai L., Udeani G.O., Slowing K. V.1., (1997),Cancer chemoprotective activity of resveratrol, a natural product derived from grapes. Science,Vol.275, pp.218–220
106. Subbaramaiah K, Chung WJ, Michaluart P, Telang N, Tanabe T, Inoue H, Jang M, Pezzuto JM & Dannenberg AJ .,(1998),Resveratrol inhibits cyclooxygenase-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. Journal of Biological Chemistry, Vol.273 pp.:21875–21882.
107. Mac Carrone M, Lorenzon T, Guerrieri P and Agro AF.(1999).Resveratrol prevents apoptosis in K562 cells by inhibiting lipoxygenase and cyclooxygenase activity. European Journal of Biochemistry, Vol.265 pp. 27–34.

108. Gautam S.C., Xu Y.X., Dumaguin M., Janakiraman N. and Chapman R.A.,(2000) ,Resveratrol selectively inhibits leukemia cells: a prospective agent for ex vivo bone marrow purging. Bone marrow transplantation, Vol. 25(6) pp.639-645
109. Surh YJ. Hurh YJ.Kang J-Y.,Lee E., Kong G and Lee SJ.,(1999),Resveratrol, an antioxidant present in red wine, induces apoptosis in human promyelocytic leukemia (HL-60) cells. Cancer Lett.,Vol.140(1-2).pp.1–10.
110. Ding XZ. and Adrian TE.,(2002),Resveratrol inhibits proliferation and induces apoptosis in human pancreatic cancer cells. Pancreas,Vol. 25(4). pp.71–6.
111. Joe A.K., Liu H., Suzui M., Vural M.E., Xiao D., Weinstein I.B.,(2002),Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. Clin Cancer Res . Vol.8(3) pp.893–903.
112. Potter GA, Patterson LH, Wanogho E, Perry PJ, Butler PC, Ijaz T, Ruparelia KC, Lamb JH, Farmer PB, Stanley LA, Burke MD.(2002),The cancer preventative agent resveratrol is converted to the anticancer agent piceatannol by the cytochrome P450 enzyme CYPIBI. Br J Cancer Vol.86 pp.774–8.
113. Huang C., Ma W-Y., Goranson A., Dong Z., (1999),Resveratrol suppresses cell transformation and induces apoptosis through a p53-dependent pathway. Carcinogenesis ,,Vol. 20(2) pp. 237–42.
114. Kundu J.K., and Surh Y.J., (2004),.Molecular basis of chemoprevention by resveratrol: NF-κB and AP-1 as potential targets. Mutat Res , Vol.555(1-2), pp.65–80.
115. Castello L., Tessitore L,(2005),Resveratrol inhibits cell cycle progression in U937 cells. Oncol Rep ., Vol.13(1) pp.133–7
116. Su, H.-C.; Hung, LM; Chen, JK ,(2006),.Resveratrol, a red wine antioxidant, possesses an insulin-like effect in streptozotocin-induced diabetic rats.AJP: Endocrinology and Metabolism ,Vol.290 (6) pp.1339.
117. Chen J., Dong XS and Guo XG.,(2009), Inhibitory effect of resveratrol on the growth of human colon cancer ls174t cells and its subcutaneously transplanted tumor in nude mice and the mechanism of action. Zhonghua Zhong Liu ZaZhi, , Vol.31 pp. 15-9
118. Vanamala J, Reddivari L, Radhakrishnan S *et al.* (2010), Resveratrol suppresses IGF-1 induced human colon cancer cell proliferation and elevates apoptosis via suppression of IGF-1R/Wnt and activation of p53 signaling pathways. BMC Cancer, Vol.10: 238. pp.1-14,
119. Bhattacharya S, Darjatmoko SR, Polans AS,(2011), Resveratrol Modulates the Malignant Properties of Cutaneous Melanoma via Changes in the Activation and Attenuation of the Anti-apoptotic Protooncogenic Protein Akt/PKB.Melanoma Res, Vol.21 pp.180-7,
120. Gokbulut AA, Apohan E, Baran Y., (2013),Resveratrol and quercetin-induced apoptosis of human 232B4 chronic lymphocytic leukemia cells by activation of caspase-3 and cell cycle arrest. Hematology, Vol.18, pp.144-50,
121. Tanu Garg,V. K. Yadav.,(2014),Effects Of Resveratrol As An Anticancer Agent – A Systematic Review. ,Int J Pharm Bio Sci ; Vol. 5,4.pp.534 – 542
122. Ariane R. Guthrie, H-H. Sherry Chow & Jessica A. Martinez.,(2017),Effects of resveratrol on drug- and carcinogen-metabolizing enzymes, implications for cancer prevention, Pharma Res Per, Vol.5(1),
123. V. Vingtdeux, U. Dreses-Werringloer, H. Zhao, P. Davies, and P. Marambaud,.,(2008), “Therapeutic potential of resveratrol in Alzheimer’s disease,” BMC Neuroscience Vol.9,(2)
124. Teng Ma, Meng-Shan Tan, Jin-Tai Yu, and Lan Tan,(2014),Resveratrol as a Therapeutic Agent for Alzheimer’s Disease BioMed Research InternationalVolume, pp.-1-13
125. Vonsattel J. P. G. and DiFiglia M..,(1998),Huntington disease, Journal of Neuropathology and Experimental Neurology, Vol. 57 (5) pp. 369–384
126. P. Kumar, S. S. V. Padi, P. S. Naidu, and A. Kumar.,(2007),Cyclooxygenase inhibition attenuates 3-nitropropionic acid-induced

neurotoxicity in rats: possible antioxidant mechanisms," Fundamental and Clinical Pharmacology, Vol.21(3) pp.297–306

127. Granzotto S., Bolognin J., Scancar R., Milacic and Zatta P.,(2011),β-amyloid toxicity increases with hydrophobicity in the presence of metal ions," Monatshefte fur Chemie,Vol. 142(4),pp. 421–430
128. V. Desquiret-Dumas, N. Gueguen, G. Leman.,(2013),Resveratrol induces amitochondrial complex i-dependent increase in nadh oxidation responsible for sirtuin activation in liver cells," The Journal of Biological Chemistry, Vol.288(51) pp.36662– 36675.
129. Tellone E., Galtieri A., Russo A., Giardina B., and Ficarra S.,(2015),Resveratrol: A Focus on Several Neurodegenerative Diseases.,Oxidative Medicine and Cellular Longevity,.Article pp. 392169:14
130. Rijk M. C., Tzourio C., Breteler M. M..,(1997),Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSONcollaborative study. EuropeanCommunity Concerted Action on the Epidemiology of Parkinson's disease," Journal of Neurology Neurosurgery and Psychiatry,Vol.62(1) pp.10–15
131. Jin F.,Wu Q., Lu Y.-F., Gong Q.-H., and Shi J.-S.,(2008),Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats. European Journal of Pharmacology, Vol.600,pp.78-82
132. Petrovski G., Gurusamy N. and Das D.K.2011.Resveratrol in cardiovascular health and disease. Annals of the NY academy of sciences, Vol.1215,pp.22-33
133. Tyagi S., Singh G., Sharma A., Aggarwal G., (2010),Clinical and Medicinal Applications Of Resveratrol: A Review. International Journal of Pharmaceutical Sciences, Vol.3(1), pp.49-52
134. Klinge C.M., Wickramasinghe N.S., Ivanova M.M. and Dougherty S.M.,(2008),Resveratrol stimulates nitric oxide production by increasing estrogen receptor and phosphorylation in human umbilical vein endothelial cells. The FASEB Journal, Vol.22 pp. 2185-2197
135. Deng JY, Hsieh PS, Huang JP, Lu LS, Hung LM., (2008),Activation of estrogen receptor is crucial for resveratrol-stimulating muscular glucose uptake via both insulin dependent and -independent pathways., Diabetes. Jul; Vol. 57(7) pp.1814-23.
136. K. Szkudelska, M. Deniziak, P. Roś,K. Gwóźdź, T. Szkudelski,,(2017),Resveratrol Alleviates Ethanol-Induced Hormonal And Metabolic Disturbances In The Rat, Physiol. Res. Vol.66,pp.135-145,
137. Soares DG, Andreazza AC, Salvador M..,(2003.), Sequestering ability of butylated hydrooxytoluene, propyl gallate, resveratrol, and vitamin C and E against ABTS, DPPH, and hydroxyl free radicals in chemical and biological systems. J Agric Food Chem Vol.51(4), pp.1077–80.
138. Jang J-H. and Surh Y-J.,(2001),Protective effects of resveratrol on hydrogen peroxide-induced apoptosis in rat phenochromocytoma. Mutat Res , Vol.496(1-2) pp.181–90.
139. Losa G.A.(2003),.Resveratrol modulates apoptosis and oxidation in human blood mononuclear cells. Eur J Clin Invest, Vol. 33(9) pp.818–23.
140. Kutuk O., Adli M., Poli G. and Basaga H., (2004.), Resveratrol protects against 4-HNE induced oxidative stress and apoptosis in Swiss 3T3 fibroblasts. BioFactors, Vol. 20(1) pp.1–10
141. Finley L.W.S. and Haigis M.C.,(2010),The coordination of nuclear and mitochondrial communication during aging and calorie restriction. Ageing Research Reviews, Vol.8,pp. 173-188.
142. Ferro M. and De Souza R.R..,(2011),The importance of resveratrol in tissue aging: a review, J. Morphol. Sci,, Vol. 28 (2) pp.77-80
143. Guarente L. and Picard F.,(2005),.Calorie restriction — the SIR2 connection. Cell , Vol.120,pp.473–482
144. Koubova J. and Guarente L.,(2003),.How does calorie restriction work? Genes Dev, Vol.17.pp.313–321
145. Howitz K. T.,(2003),.Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature, Vol. 425.pp.191–196

146. Wood, J. G., (2004),Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature , Vol.430 pp.686–689
147. Gruber J., Tang S.Y and Halliwell B.(,2007),. Evidence for a trade-off between survival and fitness caused by resveratrol treatment of Caenorhabditis elegans.; Ann N Y Acad Sci., Vol.1100(1)pp.530-42
148. Labbe A., Garand C., Cogger V. C., and Paquet E. R..,(2011),Resveratrol improves insulin resistance hyperglycemia and hepatosteatosis but not hypertriglyceridemia, inflammation, and life span in a mouse model for Werner syndrome. J. Gerontol. A Biol. Sci. Med. Sci., Vol.66.pp.264–278
149. Miller, R. A., Harrison, D. E., Astle, C. M., Baur, J. A.(2011),.Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. J. Gerontol. A Biol.Sci. Med. Sci. Vol.66, pp.191–201.
150. Barger, J. L., Kayo, T., Vann, J. M., Arias, E. B. (2008),. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in Mice. PLoS One,Vol.3, 2264.
151. Jessica Stockinger, Nicholas Maxwell, Dillon Shapiro, Rafael deCabo, Gregorio Valdez,Caloric (2017),Restriction Mimetics Slow Aging of Neuromuscular Synapses and Muscle Fibers, J Gerontol A Biol Sci Med Sci, , pp.1–8
152. Gentilli M., Mazoit J.X and Bouaziz H.,(2001),Resveratrol decreases hyperalgesia induced by carrageenan in the rat hind paw, Life Sciences,Vol.,68 (11) pp.1317–21
153. Elmali N., Baysal O., Harma A., Esenkaya I. and Mizrak B.,(2007),.Effects of resveratrol in inflammatory arthritis", Inflammation, Vol.30 (1–2) ,pp.1–6.
154. De La Lastra C.A. and Villegas I.,(2005),Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications. Vol.49(5),pp.405-30.
155. Guangxi Wang, Zhiqiang Hu, Xu Song, Qiankun Cui,Qiuting Fu, Renyong Jia, Yuanfeng Zou, Lixia Li,and Zhongqiong Yin, (2017),Analgesic and Anti-Inflammatory Activities of Resveratrol through Classic Models in Mice and Rats, Evidence-Based Complementary and Alternative Medicine,,
156. Ferreira W.F.C., Sousa J.C.F., (1998)..Microbiologia ,Vol.1.
157. Wiley JM, Sherwood LM, Wollverton CJ.,(2009). Prescott´s Principles of Microbiology. New York, NY: McGraw-Hill Higher Education.
158. Overbye KM, Barrett JF.,(2005),Antibiotics: Where did we go wrong? Drug Discovery,10: 45-52
159. Butler MS, Buss AD,2006. Natural products--the future scaffolds for novel antibiotics? Biochemical Pharmacology. Vol.71,pp.919-929.
160. Mahady GB, Pendland SL,(2000), Resveratrol inhibits the growth of Helicobacter pylori in vitro. American Journal of Gastroenterology. Vol. 95.pp.1849-1849.
161. Tegos G, Stermitz FR, Lomovskaya O, Lewis K,. (2002),Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. Antimicrobial Agents and Chemotherapy. Vol.46.pp.3133-3141.
162. Chan MM-Y., (2002),Antimicrobial effect of resveratrol on dermatophytes and bacterial pathogens of the skin. Biochem Pharmacol, Vol.63, pp.99-104.
163. Filip V., Plocková M., Šmidrkal J.S., Špičková Z., Melzoch K. and Schmidt Š.,(2003),Resveratrol and its antioxidant and antimicrobial effectiveness. Food Chem, Vol.83.pp.585 – 593
164. Michela Campagna and Carmen Rivas.,(2010),.Antiviral activity of resveratrol, Biochemical Society Transactions, part -1,38.
165. Gehm B.D., McAndrews J.M, Chien P. and Jameson J.L., (1997). Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor, Proc. National. Academy of Sciences, Vol.9;94(25).pp.14138-43
166. Docherty J.J., Sweet T.J., Bailey E., Faith S.A. and Booth T.,(2006),Resveratrol inhibition of varicella-zoster virus replication in vitro, Antiviral Research, Vol.72 (3).pp. 171–7
167. Guan W.D., Yang Z.F., Liu N., Qin S., Zhang F.X. and Zhu Y.T.,(2008),In vitro experimental

study on the effect of resveratrol against several kinds of respiroviruses. Zhong Yao Cai ,31 (9).pp. 1388–90.

168. Palamara AT, Nencioni L, Aquilano K. (2005),.Inhibition of influenza A virus replication by resveratrol". The Journal of Infectious Diseases Vol. 191(10).pp.1719–29.
169. Evers D.L, Wang X., Huong SM., Huang DY., Huang E.S.,(2004),3,4',5-Trihydroxy-trans-stilbene (resveratrol) inhibits human cytomegalovirus replication and virus-induced cellular signaling, Antiviral Research , Vol.63 (2).pp.85–95
170. Lee, W.X.; Basri, D.F.; Ghazali, A.R..(2017),Bactericidal Effect of Pterostilbene Alone and in Combination with Gentamicin against Human Pathogenic Bacteria. Molecules, Vol.22, pp.463.
171. John J. Docherty ,Ming Ming Fu and Margaret Tsai.,(2001),Resvatrol selectively inhibits Neisseria gonorrhoeae, Neisseria meningitidis,J.antimicrob Chemother, Vol.47.pp.243-244.
172. Ogungbamila,, F.O.,Onawumi ,G.O., Ibewuike , J. C and Funmilayo, K.A.(1997), Antibacterial constituents of Ficus barteri fruits.International Journal of Pharmacognosy Vol.35pp.185-9
173. Joao T., Mar L., Antonio G., Francisco A. T., María T. G. and Juan Carlos Espín. ,(2013),Resveratrol and Clinical Trials: The Crossroad from In Vitro Studies to Human Evidence ,Current Pharmaceutical Design, Vol.19.pp. 6064-6093
174. Azorín-Ortuño M, Yañéz-Gascón MJ, Pallarés FJ, Rivera J.,(2012),A dietary resveratrol-rich grape extract prevents the developing of atherosclerotic lesions in the aorta of pigs fed an atherogenic diet. J Agric Food Chem Vol.,60.pp. 5609-20.
175. Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, Beaudeux JL,(2010), Resveratrol bioavailability and toxicity in humans. Mol Nutr Food Res..pp. Vol.54,pp.7–16
176. Joana M. Planas, Helena Colom and M. Emilia Juan.,(2011),Resveratrol: A polyphenol with multiple effects, Recent Advances in Pharmaceutical Sciences.pp. 101-120
177. Juan, M.E., Buenafuente, J., Casals, I., Planas, J.M.., (2002), Plasmatic levels of trans-resveratrol in rats., Food Res. Inter., Vol.35.pp.195
178. Alfaras, I., Pérez, M., Juan, M.E., Merino, G., Prieto, J.G., Planas, J.M., Alvarez,A.I..,(2010,) J. Agric. Food Chem., Vol. 58.pp.4523
179. Muñoz O,Muñoz R and Bustamante S, (2015),Pharmacological Properties of Resveratrol. A Pre-Clinical and Clinical Review, Biochem Pharmacol,,Vol. 4 ,Issue 5
180. Almeida L, Vaz-da-Silva M, Falcão A, Soares E, Costa R, *et al.*,(2009),Pharmacokinetic and safety profile of trans-resveratrol in a rising multiple dose study in healthy volunteers. Mol Nutr Food Res Vol.53 Suppl 1.pp. 7-15.
181. Nunes T., Almeida L., Rocha JF., Falcão A and Fernandes-Lopes C.,(2009),. Pharmacokinetics of trans-resveratrol following repeated administration in healthy elderly and young subjects. J Clin Pharmacol ,Vol,,49.pp.1477-1482
182. Sharan S.and S.Nagar.,(2013),.Pulmonary metabolism of resveratrol:In vitro and in vivo evidence.Drug Metab Dispos., Vol.411.pp.1163-1169
183. Wenzel E, Somoza .,,(2005), Metabolism and bioavailability of trans-resveratrol., Mol Nutr Food Res. May; Vol.49(5).pp.472-81.
184. Boocock DJ, Faust GE, Patel KR, Schinas AM, Brown VA.(2007),.Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemo-preventive agent. Cancer Epidemiol Biomarkers Prev Vol.,16.pp. 1246-1252.
185. Brown VA, Patel KR, Viskaduraki M, Crowell JA, Perloff M ., (2010).Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: Safety, pharmacokinetics, and effect on the insulin-like growth factor axis. Cancer Res, Vol.70.pp.9003-9011.
186. Patel KR, Scott E, Brown VA, Gescher AJ, Steward WP.,(2011)Clinical trials of resveratrol. Ann N Y Acad Sci Vol.1215.pp. 161-169.

187. Augustin,M.A.,L.sanguansri and T.Lockett., (2013).Nano-and micro-encapsulated system for enhancing the delivery of resveratrol.Ann.N.Y.Acad.Sci. Vol.,1290.pp.107-112
188. Laza-Knoerr A. L., Gref R., Couvreur P..,(2010),Cyclodextrins for drug delivery. Journal of Drug Targeting. Vol. 18(9).pp.645–656.
189. Marel A.-K., Lizard G., Izard J.-C., Latruffe N., Delmas D.,(2008),Inhibitory effects of trans-resveratrol analogs molecules on the proliferation and the cell cycle progression of human colon tumoral cells. Molecular Nutrition & Food Research. Vol.52(5).pp.538–548D
190. M. Urpi-Sarda, R. Zamora-Ros, R. Lamuela-Raventos *et al*., (2007), "HPLC-tandem mass spectrometric method to characterize resveratrol metabolism in humans," Clinical Chemistry, vol. 53(2), pp. 292–299
191. James M. Smoliga , and Otis Blanchard., (2014), Enhancing the Delivery of Resveratrol in Humans:If Low Bioavailability is the Problem, What is the Solution?, Molecules Vol.19.pp. 17154-17172
192. Gehan F Balata,Ebtessam A Essa,Hanan A Shamard, Samira H Zaidan,Mohammed AS Abourehab ,(2016),Self-emulsifying drug delivery systems as a tool to improve solubility and bioavailability of resveratrol, Drug Design, Development and Therapy,Vol.10,pp. 117–128
193. Sessa, M.; Tsao, R.; Liu, R.; Ferrari, G.; Donsi, F.,(2011), Evaluation of the stability and antioxidantactivity of nanoencapsulated resveratrol during in vitro digestion. J. Agric. Food Chem. Vol.59,pp.12352–12360.
194. Ansari A., Vavia R., Trotta F. and Cavalli R.(2011),Cyclodextrin-Based Nanosponges for Delivery of Resveratrol: In Vitro Characterisation, Stability, Cytotoxicity and Permeation Study.AAPS PharmSciTech, Vol.12, pp.279–286.
195. Frozza, R.L.; Bernardi, A.; Paese, K.; Hoppe, J.B.; da Silva, T.; Battastini, A.M.; Pohlmann, A.R.; Guterres, S.S.; Salbego, C.,(2010), Characterization of trans-resveratrol-loaded lipid-core nanocapsules and tissue distribution studies in rats. J. Biomed. Nanotechnol. Vol.6, pp.694–703.
196. Guo L., Peng Y., Yao J., Sui L., Gu A and Wang J., (,2010.)Anticancer activity and molecular mechanism of resveratrol-bovine serum albumin nanoparticles on subcutaneously implanted human primary ovarian carcinoma cells in nude mice. Cancer Biother. Radiopharm., Vol. 25, pp.471–477.
197. Jose, S.; Anju, S.S.; Cinu, T.A.; Aleykutty, N.A.; Thomas, S.; Souto, E.B.,(2014),In vivo pharmacokinetics and biodistribution of resveratrol-loaded solid lipid nanoparticles for brain delivery. Int. J. Pharmaceut. Vol. 474, pp.6–13.
198. Singh, G.; Pai, R.S..,(2014.),Recent advances of resveratrol in nanostructured based delivery systems and in the management of HIV/AIDS. J. Control. Release Vol.194.pp.178–188
199. Pangeni, R.; Sahni, J.K.; Ali, J.; Sharma, S.; Baboota, S.,(2014),.Resveratrol: Review on therapeutic potential and recent advances in drug delivery. Expert Opin. Drug Deliv. Vol.11, pp.1285–1298
200. Imtiaz A. Siddiqui,, Vanna Sanna,,Nihal Ahmad, Mario Sechi, and Hasan Mukhtar, (2015) ,Resveratrol nanoformulation for cancer prevention and therapy, Ann. N.Y. Acad. Sci. Vol. XXXX.pp. 1–12
201. Pallàs, M.; Casadesús, G.; Smith, M.A.; Coto-Montes, A.; Pelegri, C.; Vilaplana, J. & Camins, A.,(2009), Resveratrol and neurodegenerative diseases: Activation of SIRT1 as the potentialpathway towards neuroprotection. Current Neurovascular Research, Vol. 6.pp. 70-81
202. Albert Y. Sun,,Qun Wang, Agnes Simonyi, Grace Y. Sun, (2010), Resveratrol as a Therapeutic Agent for Neurodegenerative Diseases, Mol Neurobiol. ; Vol. 41(2-3).pp. 375–383
203. Squillaro ,Peluso G and Melone MAB.,(2017), Nanotechnology-Based Polyphenol Delivery: A Novel Therapeutic Strategy for the Treatment of Age-Related Neurodegenerative Disorder, , Austin Aging Res ,Vol.1 Issue 1

204. Pollen K Yeung,(2017),Therapeutic Potential of Resveratrol for Cardiovascular Protection, Cardiovasc Pharm Open Access,pp. 6:2
205. D. Delmas, V. Aires, E. Limagne et al., (2011),Transport, stability,and biological activity of resveratrol," Annals of the New York Academy of Sciences, vol. 1215(1), pp. 48–59.