Acta Scientific Microbiology (ASMI)
ISSN: 2581-3226
DOI: 10.31080/ASMI.2019.S01.0005

Review Article

Special Issue 1- 2019

Will Utilization of Resveratrol's Effects be Practical in Multiple Chronic Inflammatory Diseases and Autoimmune Diseases: A Detailed Review of its Immune Responses and Further Clinical Development in Humans in Future - A Systematic Review

Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[2] and Mandeep Singh[3]

1Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Jalandhar, Punjab, India

[2]Scientific Director, Rotunda-A Centre for Human Reproduction, Mumbai, India

[3]Consultant Neurologist, Swami Satyanand Hospital, Jalandhar, Punjab, India

***Corresponding Author:** Kulvinder Kochar Kaur, Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Jalandhar, Punjab, India.

Received: August 17, 2019
Published: September 10, 2019
ISSN: 2581-3226
DOI: 10.31080/ASMI.2019.S01.0005

Abstract

Resveratrol is a very well known polyphenolic stilbenoid that exists in mulberries, peanuts, rhubarb, redwine, grapes, blueberries and in various other plants. It has been found to be of benefit in the prevention of chronic diseases that are associated with inflammation like diabetes mellitus, obesity cardiovascular diseases (CVD), neurodegeneration, cancers and many other diseases. Further Resveratrol controls immunity by interfering with control of immune cells, proinflammatory cytokines synthesis and gene expression. It affects sirtuin, adenosine monophosphate kinase, nuclear factor – B, inflammatory cytokines, antioxidant enzymes at molecular level, besides the cellular processes like gluconeogenesis, lipid metabolism, mitochondrial biogenesis, angiogenesis and apoptosis. It also represses the toll like receptor (TLR), and proinflammatory genes expression. Moreover the antioxidant action of Resveratrol and its capability to inhibit enzymes involved in the production of eicasonoids, add to its anti-inflammatory effects. Its actions on the immune system have multiple beneficial effects on health, regarding various autoimmune and chronic inflammatory diseases. The aim of this review is to get insight on how Resveratrol targets various inflammatory components and exerts immune regulatory effects on immune cells.

Keywords: Resveratrol; Macrophages; Tlymphocutes; Immune Responses; Natural Killer Cells; B lymphocytes

Abbreviations

Sirt 1: Silent Mating Type Information Regulation 2 Homolog; TLR: Toll like Receptor; STAT: Signal Transducers and Activators of Transcription; PAF: Platelet Activating Factor; TNF Alpha: Tumor Necrosis Factor Alpha; MMP: Metalloproteinases; AMPK-AMP: Activated Protein Kinase; NAD+: Nicotinamide Adenine Dinucleotide; cAMP: Cyclic Adenosine Monophosphate; CLRs: C Type Lectin Receptors; NLRs: Cytoplasmic Nucleotide Oligomerization Domain (NOD) like Receptors; RLRs: RNA Helicase Retinoic Acid Inducible Gene 1 (RIG1) like Receptors; LPS: Lipopolysaccharide; TBK 1: TANK Binding Kinase 1; TRIF: Toll-Interleukin-1 Receptor Domain –Containing Adaptor Inducing Interferon; IRE1: Inositol Requiring Enzyme 1; Xbp1: X Box Protein 1; NPRP2: Nod Like – Receptor Family, Pyrin Domain Containing 3; CREB 1: cAMP-Responsive Element Binding Protein 1; IRAK1: IL-1 Receptor Associated Kinase; TAM: Tumor Associated Macrophages; KLF-4: Kruppel Like Factor 4; TGFβ 1: Transforming Growth Factor Beta 1; MHC: Major Histocompatibility Complex; Tregs: Regulatory T Cells; SLE- Systemic Lupus Erythematosis; RORγT: Retinoic Acid – Related Orphan Nuclear Receptors; NAFT: Nuclear Factor of Activated T Cells; DIO: Diet Induced Obesity; HFD: High Fat Diet; Nrf2: Nuclear Factor Erythroid 2 Related Factor; PI3K: Phosphatidyl Inositol 3' Kinase; NK cells: Natural Killer Cells; Prf1: Perforin; GzmB: Granzyme B; FASL: FAS Ligand; CCL: CC Motif Ligand; MIP1: Monocyte Chemoattrac-

tant Protein 1; XCL1: Chemokine X-C Motif Ligand; KIR's: Killer Cell Immunoglobulin like Receptors; NKG2D: Natural Group 2, Member D; CFLIP: Cellular FLICE –Like Inhibitory Protein; APC: Antigen Presenting Cells; Bregs: Regulatory B Cells.

Introduction

Resveratrol (trans 3, 4, 5-trihydroxy stilbene) is a natural polyphene found in redwine, rhubarb, along with fruits like blue berries, many red grape varieties and peanuts, etc, which play an important role in a large variety of biological activities [1]. Resveratrol has antioxidative, anti-inflammatory, anticancer, antimicrobial, ant neurodegenerative, and estrogenic properties. By interacting with several molecule targets, Resveratrol regulates innateand adaptive immunity [2]. Yet sometimes it's properties look contrasting. Resveratrol modulates immune function in a dose dependent fashion, at low doses it stimulates the immune system, while at higher doses causes immunosuppression. It has been demonstrated that Resveratrol takes part in the activation of macrophages, Tcells and natural killer (NK) cells and is involved in CD4+CD25+regulatory Tcells suppressive functions [2]. Its effects are the result of its ability to remove reactive oxygen species (ROS), and to activate many anti-inflammatory pathways, including among others, Sirtuin-1 (Sirt 1). Sirt 1 (silent mating type information regulation 2 homolog) disrupts the TLR4 (toll like receptor 4)/NFκB/STAT (signal transducers and activators of transcription) signal, that in turn reduces cytokine production from inactivated immune cells, or macrophage/mast cell-derived proinflammatory factors like platelet activating factor (PAF), TNFα, and histamine [3]. In view of its beneficial effects regarding human health (figure 1) and for showing properties helpful in immunological disorders it is being proposed to be used as a dietary supplement for human consumption [4]. But its pharmacokinetic analysis shows that Resveratrol undergoes rapid metabolism in the body. It has very little bioavailability following oral administration, inspite of absorption of 70%, which affects the physiological validity of high concentrations used *in vitro* [5].

Methods

We carried out a search using Pubmed search engine and the MeSH like Resveratrol; Immune cells including B cells Tcells, NK cells, Macrophages, innate and adaptive immunity and beneficial effects of Resveratrol.

Results and Discussion

We found a total of 223 articles out of which we selected 50 articles for this review. No meta-analysis was done.

Immune pathways of resveratrol

A crucial function of Resveratrol is to inhibit the production of inflammatory factors via the activation of Sirt1. Sirt 1 is an important deacetylase involved in numerous molecular events, including metabolism, cancer, embryonic development and immune tolerance. Sirt 1 maintains peripheral Tcell tolerance. Ablation of Sirt 1 => increased Tcell activation and occurrence of spontaneous autoimmune disease. Resveratrol binding to Sirt 1 modulates the Sirt 1 structure and increases binding to the substrates. With the ability to activate Sirt1 and suppress inflammation, Resveratrol abrogates inflammatory symptoms in various experimental autoimmune disease models, like colitis, type 1 diabetes (T1D) encephalomyelitis, and rheumatoid arthritis (Figure 1) [6,7]. One of the major substrates of Sirt 1 is p65/Rel A, a NFκB member that is a major regulator of leukocyte activation and inflammatory cytokine signaling. Activation of Sirt by Resveratrol produces factors like TNFα, IL-1β, IL-16.

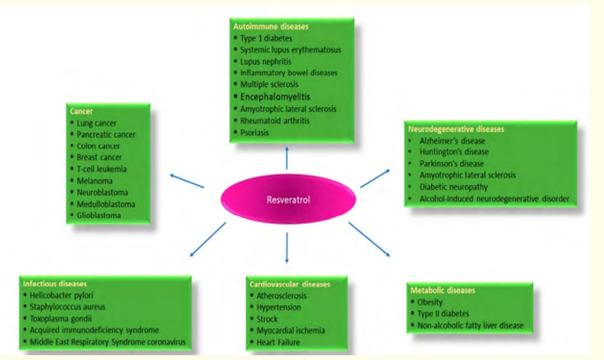

Figure 1: Courtesy ref no-50.-Activity of resveratrol against different human diseases based on experimental studies.

Metalloproteinases (MMP1) and MMP3, and Cox 2 [8] (Figure 2). Other targets of Resveratrol are AMP –activated protein kinase (AMPK), that is an integral energy sensor in cells that controls activity of Sirt 1 by regulating the cellular events of available nicotinamide adenine dinucleotide (NAD+) (figure 2). Cyclic Adenosine Monophosphate (cAMP), levels stimulate protein kinase A (PKA), that in turn phosphorylates and activates Sirt1. Genetic deletion of Sirt or by adding Sirt inhibitors like Sertinol abolishes the functions of Resveratrol, emphasizing the importance of Sirt in the anti-inflammatory properties of Resveratrol. For downstream activation of AMPK, an increase of NAD+ levels induce Sirt1 activation that promotes metabolic changes which are of benefit via deacetylation and acetylation of peroxisome proliferator –activated receptor gamma, coactivator1-alpha (PGC1-α) (Figure 2).

Macrophages and resveratrol

Resveratrol =>anti-inflammatory profile in macrophages. Macrophages differentiate from blood monocytes and take part in both adaptive and innate immunity. These cells represent a heterogenous pool of cells with multiple biological activities, based on their physical location and on receiving external signals that they get

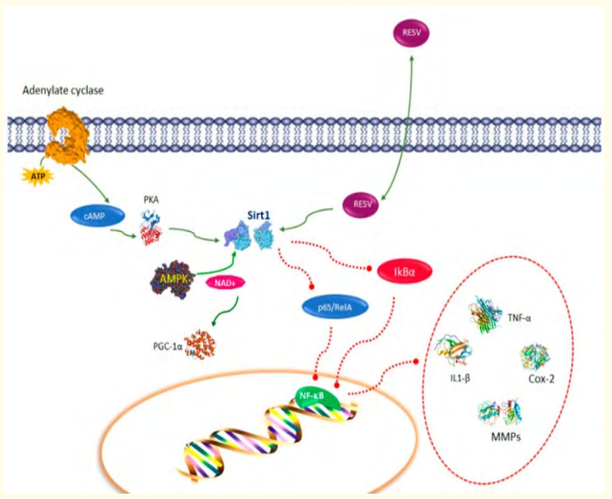

Figure 2: Courtesy ref no-50.Resveratrol pathways in immune function: resveratrol activates Sirtuin-1 (Sirt1) inhibiting RelA acetylation and promotes inhibitor protein-κBα (IkBα) degradation, which decreases nuclear factor kappa B (NF-κB)-induced expression of tumor necrosis-alpha (TNF-α), interrleukin (IL)-1β, IL(-6), metalloproteases (MMPs), and cyclooxygenase Cox-2. Cyclic adenosine monophosphate (cAMP) levels trigger protein kinase A (PKA), which activates Sirt1. AMP-activated protein kinase (AMPK) controls the activity of Sirt1 by regulating the cellular levels of nicotinamide adenine dinucleotide (NAD+). In the downstream activation of AMPK, an increase of NAD+ levels induces Sirt1 activation, which promotes deacetylation and activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α).

from the tissue microenvironment. Many of these functions appear to be divergent in nature: pro versus anti-inflammatory effects, immunogenic versus tolerogenic activities, and tissue destruction versus repair. With so many types of pattern recognition receptors (PRRs) these immune cells can specifically identify conserved pathogen associated molecular patterns (PAMPs), that are present only on microbes like viruses, bacteriaand fungi. Main members of PRR families are transmembrane TLRs, C type lectin receptors (CLRs), cytoplasmic nucleotide oligomerization domain (NOD) like receptors (NLRs) and RNA helicase retinoic acid inducible gene 1 (RIG1) like receptors (RLRs). Hence the activated intracellular signaling induces the expression of genes involved in inflammatory and/or immune response and the recruitment of phagocytic cells to the site of infection. With their capacity to recognize pathogens and activate bactericidal activities, macrophages are always working at the site of immune defense. Anti-inflammatory cytokines are synthesized by them, like IL-10 and TGFβ, and inhibit the inflammatory pathways that get mediated by TLRs [9]. TLRs initiate signaling in both innate and adaptive immune pathways. They are a highly conserved family of transmembrane proteins made up of an extracellular domain that recognizes exogenous and endogenous danger molecules and an ectodomain which activates downstream pathways. Continuous activation or dysregulation of TLRs signaling might=>occurrence of chronic pathological conditions. Resveratrol regulates the expression of TLR4 [10]. Thus it can be used for TLR mediated inflammatory responses and chronic diseases linked to TLR activation like obesity, T2DM, Fatty liver disease, Crohn's disease, rheumatoid arthritis, cardiovascular system (CVS) and neurodegenerative disorders (Figure 1). Molecular regulation of inflammatory responses is modulated by transcription factors. Resveratrol reduces NFκB activation and Cox2 expression in (lipopolysaccharide [LPS]) -induced RAW264.7 (Figure 3). Further it inhibits TANK binding kinase1 (TBK1) and receptor interacting protein (RIP1) in a toll-interleukin-1 receptor domain –containing adaptor inducing interferon (TRIF) complex in myeloid differentiation factor 88 (MyD 88) -independent signaling pathways (Figure 3). Further Resveratrol has anti –inflammatory effects via attenuation of TLR4-TRAF6, MAPK, and AKT pathways in LPS induced macrophages [11]. Endoplasmic reticulum (ER) stress =>activation of inositol requiring enzyme 1 (IRE1), which splices X box protein 1 (Xbp1) into it's functional message and ultimately=>suppressed global translation and increased chaperone activity. If the cells fail to reduce the ER load, they will undergo apoptosis. It's been pointed that IRE-1α-Xbp1 pathway is crucial for toll like receptor (TLR) -induced inflammatory cytokines production by macrophages. Xbp1 gets regulated by post translational acetylation and deacetylation mediated by the acetyl transferase p300 and deacetylase Sirt 1 respectively. Resveratrol also prevents the increase of acetylated α-tubulin that is secondary to mitochondrial damage in macrophages stimulated by inducers of the nod like –receptor family, pyrin domain containing 3 (NPRP2) inflassome (Figure 3). In view of Resveratrol influencing the production of an ideal site for the assembly of NLRP3and ASC -=>inhibition of NLRP3 inflassome activation, that might be efficacious for the therapy of NLRP3 –related inflammatoty diseases. Besides affecting the transcription of NFκB elements, Resveratrol has an effect on the transcription of STAT3 and cAMP-responsive element binding protein 1 (CREB 1). TNFα-induced activation of NFκB elements is modulated by Resveratrol. LPS –activation of monocytes and macrophages induces the NFκB dependent transcription of chemoknes like CXCL8/IL-8. CXCL-10/IP-10, CCL2-/MCP2 and CCL5/RANTES [9]. LPS increased CD14 expression. IL-1 receptor associated kinase (IRAK1) and a phosphorylated form of p38MAPKprotein. By reducing CD14 and IRAK1 expression (Figure 3), Resveratrol prevented LPS effects, but astonishingly increased the p38MAPK protein phosphorylation [12]. Also Resveratrol reduced pro-oxidant effect in the AR42 J cell line by a MyD88 dependent pathway, i.e. antioxidant effect of Resveratrol was exerted by a MyD88 dependent way which didn't involve IRAK1 or by a TRIF dependent pathway [12] (Figure 3). Sirt1 has a direct regulatory role in macrophages function during inflammation. Pro- inflammatory cytokines production, TNFα, IL-6 and

IL-1 β by macrophages from the myeloid specific Sirt 1 knockout mice is dramatically increased in response to infection and inflammation. Besides pro- inflammatory cytokines, Sirt 1 is involved in the expression of cell surface molecules like intercellular adhesion molecule (ICAM-1) to facilitate trafficking during inflammatory reponse (Figure 3). Hyperacetylation of NFκB transcription factor Rel A/p65 has been found in macrophages from myelod specific Sirt 1 knockout mice, suggesting that anti-inflammatory activity of Sirt in macrophages occurs at least partly through NFκB suppression [13].

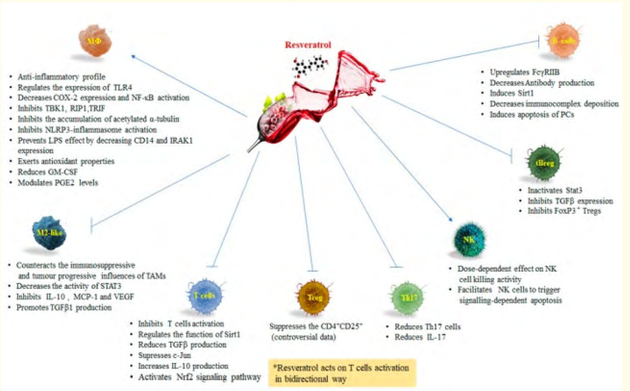

Figure 3: Courtesy ref no-50.-Effects of resveratrol on immune cells: Breg, regulatory B cell; COX2, cyclooxygenase; FOXP3, forkhead box P-3; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL-10, interleukin-10; IL-17, interleukin 17; IRAK, interleukin-1 receptor-associated kinase; LPS, lipopolysaccharide; MΦ, macrophage; MCP1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-Kappa B; NLRP3, nod-like receptor family, pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; RIP, receptor-interacting protein; PCs, plasma cells; PGE2, prostaglandin E2; Sirt1, silent mating type information regulation 2 homolog; STAT3, signal transducer and activator of transcription; TAMs, tumor associated macrophages; TBK1, TANK-binding kinase1; TGF-β1, transforming growth factor-β1; Treg, regulatory T cell; Th17, T helper 17; TRIF, toll-interleukin-1 receptor domain-containing adaptor inducing interferon; TLR-2, toll-like receptor-2; VEGF, vascular endothelial growth factor.

Also, Resveratrol markedly decreases the production of granulocyte macrophage colony stimulating factor (GMCSF) [14] (Figure 3), a pro-inflammatory cytokine which acts at the interface between innate and adaptive immunity essential for survival/differentiation/activation of pro-inflammatory macrophages and a critical marker in atheroma formation. Resveratrol modifies cell morphology, gene expression, ligand receptor interactions, signaling pathways and foam cell formation as per various studies. Moreover Resveratrol modulate the immune response by affecting cellular PGE2 levels, that plays an important role in control of immune response. Also Resveratrol upregulates COX-2 in different inflammatory disorders. Cell specific effect on IL production being another important effect of Resveratrol, increasing expression of IL-1 β and, IL-6 in peripheral blood lymphocytes (PEL's), but it has opposite effects on macrophages. Increased production of IL-1 β and, IL-6 characterizes the pro-inflammatory status, helping in T helper lymphocyte differentiation and function, but is also involved in tissue regeneration. Immune cells exposed to Resveratrol in the vascular compartment expressing significant levels of IL-1 β and, IL-6 are triggered for the adapt vs immune response. But Resveratrol affects immune response only for a limited time in view of short half life in blood, pointing that Resveratrol helps in systemic responses to injuries [9] and restrains low grade inflammatory status related to chronic diseases or tissues.

Tumor associated macrophages (TAM) and resveratrol

High infiltration of macrophages in most human cancers is associated with tumor malignancy, poor prognosis and tumor relapse. Macrophages show plasticity in their activation profile under different cytokine stimulation. They are capable of both inhibiting and promoting the growth and spread of cancers, depending on their activation state. Macrophages can be classically activated (M1) in the presence of IFNγ and LPS, while in the presence of IL-4 and IL-13, or indirectly via Th2 cells induction towards alternatively activated macrophages (M2). Macrophages Polarization changes the properties of these cells remarkably. The M1 polarized Macrophages synthesize high levels of pro- inflammatory cytokines and promote Th1 responses, that contribute to tumoricidal activity and antitumor immunity [42]. Polarization of M1 Macrophages get regulated by distinct transcriptional networks consisting of an interferon regulatory factor (IRF-1/5), STAT1/4 an NFκB [15]. Polarization of M2 Macrophages, that produce secretory factors for promoting tissue remodeling, immune tolerance and angiogenesis might be linked to tumor progression. M2 polarization is induced by Th2 cytokines, like IL-13and IL-14 [15], and is regulated by transcription factors like IRF4, STAT3/6, PPARγ and Kruppel like factor 4 (KLF-4). Evidence shows that Macrophages either executing tumor promoting or tumor suppressing activities depend on their subphenotype, that is dynamically switched [16]. TAM's in malignant tumors resemble alternatively activated macrophages (M2-like). They increase anti-tumor immune responses [17]. High density of TAM's especially the M2 subsets, matches to worse overall survival (OS) in patients with lung cancer, gastric cancer or breast cancer [18]. TAM's infiltrated in primary tumors or metastatic sites have a key role in directing tumor cells from the primary site to distant sites to distant tissues in different murine models [19]. TAM's in the peripheral blood may mediate circulating tumor cells to move and reach the distant metastatic sites [20]. Treating with a synthetic Resveratrol HS-1793, in an *in vitro* model that was trying to evaluate macrophage morphology and functions in relation to

the tumor microenvironment, significantly increased IFNγ, that reprogrammed the M2 phenotype. Hence it was proved that HS-1793 counteracted the immunosuppressive and tumor progressive affect of TAM's [21]. STATs are cytoplasmic transcription factors which act as intracellular effectors of cytokine and growth factor signaling pathways. STAT3, a member of STAT family, plays a key role in promoting proliferation and differentiation, antiapoptosis or cell cycle progression. Constitutive STAT3 activation gets involved in different tumor cells. In the M2 subset STAT3 results in tumor induced immunosuppression and constitutively activates STAT3 murine models of carcinogenesis, tumor progression is often related with a phenotype switch from M1 to M2 in TAM' s [16]. Inhibiting STAT' s signaling pathways might suppress tumor growth and metastases by inhibiting M2 like polarization of macrophages, that further points that TAM's are a possible target in cancer therapy. In lung cancer, Resveratrol therapy reduces the STAT3 activity along with inhibition of lung cancer progression by suppressing the protumor activation of TAM's [22] (Figure 3). Additionally, in a mouse lung cancer xenograft model Resveratrol markedly inhibits tumor growth, reducing cell proliferation and expression of p-STAT3 in tumor tissues [22]. While other publications showed that both antitumor and anti-metastatic effects of Resveratrol were partially due to antilymphangiogenesis through the regulation of M2 macrophages activation and differentiation [23]. Resveratrol, actually inhibited the production of IL-10 of MCP-1 in M2 macrophages, while it promoted TGFβ 1 synthesis. Still Resveratrol inhibited the phosphorylation of STAT3 without affecting its expression in the differentiation process of M2 macrophages. Moreover, a Resveratrol treated condition medium of M2 macrophages inhibited VEGFC-induced human lymphatic endothelial cells (HLEC's) migration, invasion, and lymphangiogenesis (Figure 3). Resveratrol *in vivo* inhibited tumor growth and metastases to the lung, and decreased the area of lymphatic endothelial cells in tumors [23].

T Lymphocytes and resveratrol

Effective adaptive immunity getting improved is much more longlasting and one can rely on the T and B lymphocyte responses cooperating with APC in peripheral lymphoid tissue over the course of days and weeks. Once the adaptive immune responses occur Th1and Th17, subsets of effector T helper cells, migrate from lymphoid tissue into circulation, infiltrate infective sites and produce their own cytokines enriching macrophages and neutrophils activity respectively. Innate and adaptive immunity, both their abilityto control inflammation and develop self and nonself discrimination. During development immature T cell populations acquire the ability to express antigen specific receptors which distinguish self or nonself molecules. In the thymus developing T1 lymphocytes with T cell receptors (TCRs) are capable of high affinity recognition of self peptides in the context of self, with major histocompatibility complex (MHC) proteins undergo apoptosis in a negative selection]. Playing safe against self reactive Tcells entry into periphery lymphoid tissue, regulatory T cells (Tregs) are produced naturally (nTregs) during central development of Tcells in the thymus and are induced peripherally (iTregs) during the progression of immune responses. Failing tolerance within adaptive immune system is not common, but, if activation gets involved many autoimmune diseases result. Abnormal T cell activation is involved in many autoimmune diseases, like insulin -dependent diabetes, rheumatoid arthritis, systemic lupus erythematosis (SLE), multiple sclerosis. Knowing that Resveratrol can inhibit T cell activation and decrease cytokine production, it is possible that that it might prevent autoimmune disease progression, Resveratrol treated mice show markedly decreased incidence of the disease and footpad thickness. On histopathology, infiltrated cells in the joint were definitely decreased in the Resveratrol treated mice in contrast to control mice. This finding showed that Resveratrol can prevent the development of collagen –induced arthritis [7]. The Th17 cells are CD4+T subsets, their development depends on signals mediated by IL-6, TGFβ, IL-21 and IL-23 and by induction of the lineage specific transcription factors, retinoic acid –related orphan nuclear receptors (RORγT). Unlike Th1 and Th2 cells, which after differentiation are secretory cells, Th 17 cells maintain their stem cell like properties, that allow them to last for a long time while still having the ability of producing functional divergent progeny on reactivation by antigen [24]. Th 17 cells are crucial initiators of proinflammatory responses, by recruiting neutrophils and macrophages to injured tissues and through production of IL-17, play an important role in host defence against infection to extracellular pathogens. Besides IL17, IL-23 is another cytokine produced by Th17, that controls survival and maintenance of the Th 17 phenotype and is responsible for the crosstalk between innate and adaptive immunity. Further Th17 cells produce IL-22 that is similar to IL-17, in benefitting the host in many infectious and inflammatory disorders. Synergistically, with IL-17, it can play an important role in disease due to its proinflammatory properties. Chronic inflammatory response is powerfully induced by Th17. Further in autoimmune diseases Th 17cells have an important role. Resveratrol can manipulate murine collagen –induced arthritis by inhibiting Th17 and B cells function [9]. Resveratrol 's arthritis protective effect are combined with a decreased numbers of Th17 cells and thus production of IL-17 in the draining lymph node (Figure 3) [9]. Protection against experimental immune encephalomyelitis (EAE) by Resveratrol is not associated with the decrease of $IL17^+$ T cells but is associated with increases in $IL17^+$/IL 10^+ T cells and CD-$IFN\gamma^+$ and with suppressed macrophage IL-6 and IL-23 p40 expression [25]. The function of Resveratrol on Treg cells seems to gain from Tcell activation, $CD4^+CD25^+Foxp3^+$cells were significantly decreased in total splenocytes as in tumor tissues from HS-1793-administered mice, and the production of TGFβ induced Treg showed a similar pattern. Resveratrol administration suppresses $CD4^+CD25^+$cell population among $CD4^+$cells, downregulates the secretion of TGFβ and enhances IFNγ expression in $CD8^+$T cells both *ex vivo* and *in*

vivo=>immune stimulation. Also Resveratrol reduces the expression of CD28 and CD80 and increases the production of IL-10, but does not affect the percentage of $CD4^+CD25^+$T reg cells [2] (Figure 3). Hence reported studies on Resveratrol effect on Tcells and its particulat molecular mechanisms are controversial in some cases. Sirt is involved in periphery Tcell tolerance [23], ablating Sirt in Tcells could =>hyperactivation of T cells and hence cause spontaneous autoimmune diseases [26] (Figure 3). Resveratrol inhibits T cell activation and production of antigen –specific antibody *in vivo*. Inhibition of T cell activation by Resveratrol is mediated by Sirt1 as shown by observation that the inhibitory effect of Resveratrol on T cell activation disappeared on Sirt1 knockdown Tcells. Further Sirt 1 expression was upregulated in activated T cells and was > in Resveratrol treated T cells than in naïve T cells. Further data showed that Resveratrol maintains T cell tolerance in mice by regulating the function of Sirt1 that inhibits activation of self reactive T cells which escape negative selection in the thymus. Part of the mechanism of Resveratrol modulating T cell activation, is that Resveratrol increased Sirt1 acetylase activity on c-Jun, but not on the nuclear factor of activated T cells (NAFT) and NFκB in Tcells [27]. But Resveratrol cant reduce the acetylation of cJun in Sirt1-/- T cells, that strongly pointed that acetylation change of c Jun is completely dependent on Sirt1. On activation of T cells cJun translocates into the nucleus. But the action of cJun is suppressed by Resveratrol-treated T cells (Figure 3). Hence Resveratrol clearly inhibits T cell activation by increasing the expression of Sirt 1 and the deacetylase activity of Sirt1 or cJun, that in turn blocks the translocation of cJun into the nucleus [28]. Moreover Resveratrol suppresses the protein kinase Cθ inperipheral blood T lymphocytes in a rat liver transplantation model.

Obesity has a bad impact on cell mediated immunity and increases the risk of infectious diseases. Obesity dysregulates Tcell generation and functionimpairing the ability to promotea peripheral T cell mediated protective immune response and damages wound healing and increases infection [29]. How Resveratrol can reverse the deleterious effect s of T cell function in diet induced obesity (DIO) has been demonstrated in various murine models. Resveratrol, as a supplement for HFD relieves oxidative stress, inhibits inflammatory gene expression and increases T regs number through arylhydrocarbon receptor activation in high fat diet (HFD) induced obese mice [30] (Figure 1). Moreover Resveratrol reduces the fasting blood glucose and fasting plasma insulin and increased the $CD3^+CD4^+/CD^3CD8^+$ ratio is usually associated with malignancies or the attack of a virus like HIV infection [31] (Figure 1). This decrease was also present in mouse model of SLE, which points that Resveratrol might act in these diseases inducing $CD3^+CD4^+/CD^3CD8^+$. Further Resveratrol activates nuclear factor erythroid 2 related factor (Nrf2) signaling pathway-mediated antioxidant enzyme expression and alleviates the inflammation by protecting against oxidative damage and T lymphocyte subset related chronic inflammatory response in the development of HFD obesity [30] (Figure 1). Thus Resveratrol supplement –maintained glucose homeostasis by activating the phosphatidyl inositol 3' kinase (PI3K) and SIRT1signaling pathways. In toto these observations suggest that Resveratrol can be used in the OPD to treat inflammation induced by T cell activation in a bidirectional way: for autoimmune disease model it exerts an inhibitory function, while for tumor model it decreases the suppressive function of Tregs, inhibiting the tumor growth.

Natural killer cells and resveratrol

NK cells constitute about 15% of all lymphocytes, can lyse cancer cells *in vitro* without needing prior activation. Mainly they help the host in early defense against both allogenic and autologous cells following viral infection, infection with bacteria or parasites against tumor cells. NK cells express different PRRs like TLRs, NLRs and RLRs. They respond to PAMP's in a suitable milieu in the presence of cytokines like IL2, IL-12, 1L-15 or IL-18. Subsequently, activated NK cells increase IFNγ, GM-CSF, TNFα or cytotoxic granules directed towards a target cell. Thus NK cells kill target cells through a variety of mechanism. i) NK cells form an immune synapse. Then they release cytoplasmic granules, organelles containing perforin (Prf1), the saposin like family member granulysin, and serin-protease like granzyme B (GzmB) to cleave various procapsases, that trigger epoptosis in the target cell. Also the expression of members of TNF family like the FAS ligand (FASL), TNF and TNF related apoptosis inducing ligand (TRAIL) induce tumor cell apoptosis on formation of immune synapses. ii) Secretion of a number of effector cytokines like IFNγ, IL-5, IL-10, IL-13 and GM-CSF following achieving different stages of NK cell differentiation. Besides that NK cell secrete number of chemokines that include CC motif ligand (CCL), like CCL2, CCL3, CCL4, CCL5, Monocyte chemoattractant protein (MIP1α) and (MIP 1β), RANTES, Chemokine X-C motif ligand (XCL1, lymphotactin) and IL-18. NK's interacting with other immune cells like dendritic cells in areas of inflammation modulate the innate and adaptative immune response and promote T cell response against tumors. The killing capacity against malignant cells depends on stimulation of 2 main structural classes of NK cell surface receptors like receptors of the C type lectin –like Family and their killer cell immunoglobulin like receptors (KIR's), that inhibit and/or activate signaling cascades. Some human activating receptors like different KIR's or natural cytotoxicity receptors (NCRs) like NKp30, NKp44, NKp46, and NKp80 activate signal via protein tyrosine kinase –dependent pathways. For antagonizing NK cell activation, inhibitory surface receptors like different KIR'sare present in humans, that act via protein tyrosine kinase – dependent pathways. Resveratrol has a direct effect on the ability of killing of NK cells and simultaneously affecting other immune cells like $CD\ 8^+$and $CD4^+$T cells [32]. Resveratrol can boost NKs activity against aggres-

sive cell leukemia and lymphoma by inhibiting constitutively active signal transducers and activators of transcription (STAT3) signaling. NK cell killing ability has been found in human immortalized myelogenous leukemia K562 cells. NK cell cytotoxic activity was increased at low Resveratrol concentration, while suppressed at high concentration [32]. Inhibition of viability and increased apoptosis of NK cells on incubation with high Resveratrol concentrations, while upregulation of NKG2D and IFNγ and increased NK cell killing towards leukemia K562 target cells were the findings of other researchers [33] (Figure 3). Thus a concentration dependent biphasic effect of Resveratrol, that is caused by stimulating cell apoptosis through caspase signaling pathways in high concentration ranges. This is confirmed by a markedly decreased rate of apoptotic/necrotic cells after pretreatment with the caspase inhibitor z-VAD-FMK. Further this study revealed that higher cytotoxic suscebtibility of Jurkat cells, a human lymphoblastoid T cells line, towards Resveratrol. Dose dependent enhancement of cytotoxic NK cell killng activity was also seen against tumor cell lines derived from solid tumors, like HepG2 and A59 cells after pre-stimulation of immortalized NK cells (NK-92 cells) with Resveratrol at low concentrations [34]. Moreover NK92 Resveratrol treatment induces phosphorylation of ERK1/2 and JNK and a dose dependent upregulation of perforin expression [35]. In another work, an increase in NK cell killing activity with a consequent anticancer effect was seen in a study examining the anti-infectious properties of Resveratrol in a murine acute pneumonia model [36]. An increased alveolar macrophage infiltration, increased NK cell activity, a decreased bacterial burden in the lungs and a reduced mortality was observed in the Resveratrol treated group. Isolated spleen NK cells of rats pretreated with Resveratrol showed an increased killing efficacy against YAC-1 target cells. Further Resveratrol treatment makes promyeloblastic leukemia KG-1a cells susceptible to cytokine induced killer mediated cytolysis through an increase in cell –surface expression of natural group 2, member D (NKG2D) ligands and receptor DR4, combined with a downregulation of cell surface expression of DcR1 in KG1acells, and an activation of the TRAIL pathway [37] (Figure 2). Resveratrol upregulates the agonistic receptors DR4 and DR5 in androgen –insensitive human prostate carcinoma cells PC3 and DU-145 [38], increasing TRAIL sensitivity and probably facilitating NK-cell mediated killing. Also in human prostate adenocarcinoma LNCa P cells and on PC-3 prostate cancer cells TRAIL resistant, similar results were seen after treatment with Resveratrol, i.e an increased DR4 and DR5 surface expression. A dose dependent action of caspase 3 for Resveratrol treatment alone, and caspase -8 activation for combined treatment with Resveratrol and TRAIL was seen also. Human 1205 LU metastatic melanoma cells display a Resveratrol-dependent increased sensitivity to TRAIL via downregulation of the antiapoptotic proteins cellular FLICE –like inhibitory protein (CFLIP) and Bcl-xL [39]. Further Resveratrol sensitizes to TRAIL-induced apoptotic cell death various other cancer cell types like pancreatic, breast, colon cancers, T cell leykemia, melanoma neuroblastoma, medulloblastoma, and glioblastoma [40]. Resveratrol is able to increase CD95L expression on HL 60 human leukemia cells and on T47D breast carcinoma cells [41] (Figure 3) facilitating NK cells to trigger signaling dependent apoptosis. In view of tumor cell patelet aggregation, circulating tumor cells coated by aggregated platelets could escape the immune response aiding the occurrence of metastases. Cancer cells can activate platelets and their aggregation, which correlate with their metastatic potential [26]. A connection of platelet aggregation and the susceptibility of cancer cells to NK cell mediated lysis has been documented [42]. Resveratrol inhibits platelet aggregation through reduction of integrin gp IIb/IIIa on the plasma membrane, that acts as a fibrinogen receptor involved in clot formation, which generates bridges in between platelets. Resveratrol decreases the generation of TxA2, that activates platelets and thus increases aggregation via inhibition of COXI-dependent pathways [43].

B Lymphocytes and resveratrol

B cells are characterized by their capacity to produce antibodies. Besides that they release cytokines and act as secondary APC. Their are distinct subpopulations of B cells that do both regulatory and pathogenic functions. Regulatory B cells (Bregs) are a rare subpopulation of B cells (<10%of total B cells in circulation) with regulatory/suppressor functions and are important for the peripheral tolerance mechanisms [44]. Their regulatory activity is generally, but not exclusively performed by IL-10 generation. <20% of these cells from the different subsets are IL-10 producers after stimulation. Inflammation induces potently BRegs development and differentiation. A combination of different molecules including TLRs, CD40, and B cell receptor, CD80, CD86, and cytokines are needed to activate BRegs [44]. Three different forms for B cells have been characterized on the basis of activation pathways: innate BRegs requiring signaling through innate receptors, like TLR; immature BRegs requiring CD40 stimulation; antigen specific BRegs needing both B-cell receptor and CD40 signaling. BRegs prevent inflammation by inhibition of Th1 cells activation, maintenance of the Treg cell population and Th 17 proliferation and differentiation. Though IL-10 is a crucial player in B reg inhibition of inflammation, newer investigations have shown that some Treg subsets perform their suppressive function via additional factors. Cancer metastasis needs the involvement of regulatory immune cells, like Fox P3+Tregs, a process which needs TGFβ expression (Figure 2) [45]. This study pointed that low doses of Resveratrol can be used to induce antitumor effector and to combat cancer escape mediated by tBregs [45]. It has been shown recently that Resveratrol therapy can abrogate lupus nephritis in MRL/lpr mice by upregulating FcγRIIB, =>a selective decrease in Bcells in the spleen and bone marrow [46]. Further plasma cells expressing the highest level of FcγRIIB were significantly decreased in both spleen and the bone marrow in response to Resveratrol (Figure 3). Deleting autoreactive plasma cells causes a decrease of autoantibody generation, thereby=>reduced immune

complexea deposition in the kidney. Importance of this is because neither antiproliferative agents, e. g. cyclophosphamide, nor anti CD20MABs, like rituximab, can efficiently eliminate plasma cells from bone marrow of SLE patients [46] (Figure 3). Furthermore it has been demonstrated that Sirt1 induced by Resveratrol inhibits E cell proliferation and autoantibody production, ameliorating SLE in a mouse model of constitutive and continued activation of Th1 cells [47]. Lupus nephritis is characterized by glomerular and tubulointerstitial inflammation and mesangial cell proliferation, followed by progressive glomerulosclerosis and interstitial fibrosis between tubules. Resveratrol markedly decreased fibrosis in both glomeruli and tubulointerstitial space and significantly restored glomerular morphology [47]. Additionally the degree of immunocomplexes deposition in the glomerulus was markedly decreased. The inhibitory effect of enriched FcγRIIB expression to execute a self regulatory feedback loop to control the number of plasma cells through immunocompetence dependent apoptosis. This effect is of clinical relevance in that decreased surface FcγRIIB expression on memory B cells and PCs is often seen in SLE patients, =>a limited ability to restrain B cells from activation and to induce apoptosis of PCs [48]. Thus the pharmacological upregulation of FcγRIIB expression by Resveratrol can produce a marked reduction in PC's and autoantibody generation. Thus this depletion of autoreactive PC's in the bone marrow following resveratrol therapy is mainly mediated by the FcγRIIB-dependent apoptotic pathway, instead of the inhibition of B cell receptor (BC) R-dependent activation [47]. While other studies FcγRIIB downregulation of surface FcγRIIB on their memory B cells and PC's [45]. Additionally it was shown that NFκB is a key regulator of Resveratrol in the upregulation of FcγRIIB expression [46]. Since neither Tcells nor NK cells express FcγRIIB, the selective modulation of humoral immunity via FcγRIIB, stresses on being an exclusive strategy for SLE without affecting other immune functions and avoiding the side-effects of systemic immunosuppression induced by current treatments [48].

Conclusions

Multiple experimental studies have proven by both *in vivo* and *vitro* studies that emphasize how Resveratrol controls immune mechanisms and has an immunomodulatory role. As per this work Resveratrol might be of great benefit in both preventing and treating a variety of chronic diseases, that include CVS, inflammatory, metabolic, neurological, skin diseases and different infectious diseases (figure1). Further it has an effective chemosensitizing efficacy in different cancers as proved by multiple studies. But there are some studies that are contradictory, saying that Resveratrol can function as an antagonist as well. Effects of Resveratrol vary with the situation like Resveratrol might affect chemokines and cytokines in an opposite way in various tissues. Despite preclinical studies giving very exciting data, still many queries remain Regarding the use of Resveratrol in clinical practice, in view of clinical evidence that Resveratrol is efficacious as a therapeutic option in humans are still not present. Further some systematic clinical trials that used Resveratrol therapy in humans gave disappointing results, besides the problems of clinical application of Resveratrol are huge, likeits poor water solubility, bioavailability and dosage. Hence different strategies are being tried, that include developing Resveratrol analogues [49,50] and formulations like adjuvants, nanoparticles, liposomes, micelles and phospholipid complexes for improving its bioavailability. Additionally, various other approaches have been utilized for increasing its bioavailability, that are changing its route of administration and obstructing the metabolic pathways through co-treatment with other agents. Rather, in view of several intracellular targets of Resveratrol, more work is required for finding out the ultimate effects of interactions of the synergistic effects between other polyphenols and vitamins, amino acids and other micronutrients or normally used drugs. Thus need of the hour is greater well controlled preclinical and clinical trials, for finding out the efficacy of these new formulations in comparison to the parent compound. Hopefully these future studies will offer a cutting edge therapeutic method to prevent and treat several auto immune and chronic inflammatory diseases.

Bibliography

1. Piotrowska H., *et al*. "Biological activity of piceatannol Leaving the shadow of resveratrol". *Mutation Research* 750.1 (2012): 60-82.

2. Svajger U and Jeras M. "Anti-inflammatory effects of reveratrol and its potential use in therapy of immune mediated diseases". *International Reviews of Immunology* 31.3 (2012): 202-222.

3. A larcon De La Lastra C and Villegas I. "Resveratrol as an anti-inflamm atory and antiaging agent Mechanisms and clinical implications". *Molecular Nutrition and Food Research* 49.5 (2005): 405-430.

4. Mei YZ., *et al*. "Biocatalysis and biotransformation of resveratrol in micro-organisms". *Biotechnology Letters* 37.1 (2015): 9-18.

5. Baur JA and Sinclair DA. "Therapeutic potential of resveratrol: The in vivo evidence". *Nature Reviews Drug Discovery* 5.6 (2006): 493-506.

6. Lee SM., *et al*. "Prevention and treatment of diabetes with resveratrol. In a nonobese mouse model of type1 diabetes". *Diabetologia* 54.5 (2011): 1136-1146.

7. Xuzhu G., *et al*. "Resveratrol modulates murine collagen induced arthritis by inhibiting Th 17and B cell function". *Annals of the Rheumatic Diseases* 71.1 (2012): 129-135.

8. Yamamoto Y and Gaynor RB. "Therapeutic potential of inhibiton of NFκB pathway in the treatment of inflammation and cancer". *Journal of Clinical Investigation* 107.2 (2001): 135-142.

9. Arango Duque G and Descoteaux A. "Macrophage cytokines: Involvement of immunity and infectious diseases". *Frontiers in Immunology* 5 (2014): 491.

10. Yang Y., *et al*. "Reveratrol reduces the proinflammatory effects and lipopolysaccharide –induced expression of HMGB1 and TLR4 in RAW264. 7 cells". *Cellular Physiology and Biochemistry* 33.5 (2014): 1283-1292.

11. Jakus PB., *et al*. "TRAF6 is functional in inhibition of TLR 4 mediated NFκB activation by Resveratrol". *The Journal of Nutritional Biochemistry* 24.5 (2013): 819-823.

12. Sebai H., *et al*. "Protective effect of resveratrol against LPS-induced extracellular lipoperoxidation in AR42J cells partly via Myd 88-dependent signaling pathways". *Archives of Biochemistry and Biophysics* 495.1 (2010): 56-61.

13. Schug TT., *et al*. "Myeloid deletion of SIRT 1 induces inflammatory signaling in response to environmental stress". *Molecular and Cellular Biology* 30.19 (2010): 4712-4721.

14. Schwager J., *et al*. "Resveratrol distinctly modulates the inflammatory profiles of immune and endothelial cells". *BMC Complementary and Alternative Medicine* 17.1 (2017): 309.

15. Hageman T., *et al*. "Re-educating ''tumor associated macrophages by targeting NF-kappa B". *The Journal of Experimental Medicine* 205.6 (2008): 261-268.

16. Qian BZ and Pollard JW. "Macrophage diversity enhances tumor progression and metastasis". *Cell* 141.1 (2010): 39-51.

17. Sica Aetal. "Tumor associated macrophages are a distinct M2 polarised population promoting tumor progression, Potential targets of anticancer therapy". *European Journal of Cancer* 42.6 (2006): 717-727.

18. Yin S., *et al*. "The Prognostic and Clinicopathological significance of Tumor associated macrophages in patients with gastric cancer: A Meta-analysis". *PLOS ONE* 12.1 (2017): e0170042.

19. Kitamura T., *et al*. "CCL2-induced chemokine cascade promotes breast cancer metastasis by enhancing retention of metastasis associated macrophages". *The Journal of Experimental Medicine* 212.7 (2015): 1043-1059.

20. Wang J., *et al*. "Novel mechanism of macrophage-mediated metastasis revealed in a zebrafish model of tumor development". *Cancer Research* 75.2 (2015): 306-315.

21. Jeong SK., *et al*. "Interferon gamma induced by Resveratrol analog, HS-1793, reverses the properties of Tumor associated macrophages". *International Immunopharmacology* 22.2 (2014): 303-310.

22. Sun L., *et al*. "Resveratrol inhibits lung cancer growth by suppressing M2 like polarization of tumor associated Macrophages". *Cellular Immunology* 311 (2017): 86-93.

23. Kimura Y and Sumiyoshi M. "Resveratrol Prevents Tumor Growth and Metastasis by Lymphangiogenesis and M2 Macrophage Activation and Differentiation in Tumor associated macrophages". *Nutrition and Cancer* 68.4 (2016): 667-678.

24. Caza T and Landas S. "Functional and phenotype plasticity of CD4(+)T Cell subsets". *BioMed Research International* (2015): 521957.

25. Nakayama H., *et al*. "Resveratrol induces apoptosis MH-7A human rheumatoid arthritis synovial cells in a sirtuin 1 dependent manner". *Rheumatology International* 32.1 (2012): 151-157.

26. Zhang J., *et al*. "The type III histone deacetylase Sirt 1 is essential for maintenance of Tcell tolerance in mice". *Journal of Clinical Investigation* 119.10 (2009): 3048-3058.

27. Chen X., *et al*. "Intercellular interplay between Sirt signaling and cell metabolism in immune cell biology". *Immunology* 145.4 (2015): 455-467.

28. Zou T., *et al*. "Resveratrol inhibits CD4+T cells activation by enhancing the expression and activity of Sirt1". *PLOS ONE* 8.9 (2013): e75139.

29. Karlsson EA., *et al*. "Diet induced obesity impairs the T cell memory response to influenza virus infection". *The Journal of Immunology* 184.6 (2010): 3127-3134.

30. Wang B., *et al*. "Regulatory effects of Resveratrol on glucose metabolism and T Lymphocyte subsets in the development of high fat diet induced obesity in C57BL/6 mice". *Food and Function* 5.7 (2014): 1452-1463.

31. Liu LL., *et al*. "Analysis of lymphocyte subsets in HIV negative neurosyphilis patients". *Diagnostic Microbiology and Infectious Disease* 75.2 (2013): 165-168.

32. Falchetti R., *et al*. "Effects of Resveratrol on human immune cell function". *Life Sciences* 70.1 (2001): 81-96.

33. Li Q., *et al*. "Concentration dependent biphasic effects of Resveratrol on human natural killer cells". *Journal of Agricultural and Food Chemistry* 62.45 (2014): 10928-10935.

34. Lu CC and Chen JK. "Resveratrol enhances perforin expression and NK cell cytotoxicity through NKG2D dependent pathways". *Journal of Cellular Physiology* 223.2 (2010): 343-351.

35. Chen X., *et al*. "Many NK cell receptors activate ERK2 and JNK1 to trigger microtubule organizing center and granule polarization and cytotoxicitity". *Proceedings of the National Academy of Sciences of the United States of America* 104.15 (2007): 6329-6334.

36. Lu CC., *et al*. "Resveratrol ameliorates Serratia marcescence induced acute pneumonia in rats". *Journal of Leukocyte Biology* 83.4 (2008): 1028-1037.

37. Hu L., *et al*. "Resveratrol sensitized leukemia stem cells like KG-1a cells to cytokine induced killer cells –mediated cytolysis throughNKG2D ligand and TRAIL receptors". *Cancer Biology and Therapy* 13.7 (2012): 516-526.

38. Shankar S., *et al*. "Molecular mechanismsof Resveratrol(3, 4, 5 trihydroxy –trans-stilbene)and its interactions with TNF related apoptosis inducing ligand(TRAIL) in androgen –insensitive prostate cancer cells". *Molecular and Cellular Biochemistry* 304.1-2 (2007): 273-285.

39. Ivanov VN., *et al*. "Resveratrol sensitizes melanomas in TRAIL through modulation of antiapoptic gene expression". *Experimental Cell Research* 314.5 (2008): 1163-1173.

40. Jacquemin G., *et al*. "Combining naturally occurring polyphenols with TNF-related apoptosis –inducing ligand: A promise approach to kill resistant cancer cells?". *Cellular and Molecular Life Sciences* 67.18 (2010): 3115-3130.

41. Clement MV., *et al*. "Chemopreventive agent Resveratrol, a natural product derived fromgrapes, triggers CD 95 signalling –dependent apoptosis in human tumor cells". *Blood* 92.3 (1998): 996-1002.

42. Nieswandt B., *et al*. "Lysis of tumor cells by natural killer cells in mice is impeded by platelets". *Cancer Research* 59.6 (1999): 1295-1300.

43. Toliopoulos IK., *et al*. "Resveratrol diminishes platelet aggregation and increases susceptibility of K562 tumor cells to natural killer cells". *Indian Journal of Biochemistry and Biophysics* 50.1 (2013): 14-18.

44. Mauri C and Menon M. "Human regulatory B cells in health and disease: Therapeutic potential". *Journal of Clinical Investigation* 127.3 (2017): 772-779.

45. Lee Chang C., *et al*. "Inhibition of breast cancer metastasis by Resveratrol-mediated inactivation of tumor evoked regulatory B cells". *The Journal of Immunology* 191.8 (2013): 4141-445.

46. Jhou JP., *et al*. "Upregulation of FcγRIIB by Resveratrol via NFκB activation reduces B cell numbers and ameliorates lupus". *Experimental and Molecular Medicine* 49.9 (2017): e381.

47. Wang ZL., *et al*. "Resveratrol Possesses protective effects in a pristane –induced lupus mouse model". *PLOS ONE* 9.12 (2014): e114792.

48. Isaak A., *et al*. "Physiological upregulation of inhibitory receptors FcγRII and CR1 on memory B cells is lacking on SLE patients". *International Immunology* 20.2 (2008): 185-192.

49. Jeandet P., *et al*. "Engineering stilbene metabolic pathways in microbial cells". *Biotechnology Advances* 36.8 (2018): 2264-2283.

50. Malaguatnera L. "Influence of Resveratrol on the Immune Response". *Nutrients* 11.5 (2019): 946.