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Resveratrol and vitamin D: Significant potential interpretative problems arising from their mutual processes, interactions and effects

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ABSTRACT

The hypothesis is formulated and presented that resveratrol and vitamin D have important mutual processes, interactions and induced effects that if not taken into account could seriously jeopardize the interpretation of their current and future preclinical, epidemiological and clinical studies. In support of this hypothesis, evidence is presented that resveratrol and vitamin D mutually share some of the same biochemical processes and mechanisms as well as the fact that they can each affect some of the same diseases and maladies.

Introduction

Both resveratrol and vitamin D are currently the subjects of intense biological and medical interest. While their individual biological mechanisms and processes have been and are being intensively investigated, until now such investigations have most often been carried out separately and compartmentalized without considering their possible mutually synthesized interactions and effects. It is hypothesized that resveratrol and vitamin D have important potential interactions that could seriously affect their preclinical (both *in vitro* and *in vivo*), epidemiological and clinical studies. In this regard, vitamin D whether produced in the skin by solar radiation or through dietary intake, could seriously affect resveratrol. Three sections of this report are being presented in support of this hypothesis: consideration and description of the biochemical processes undergirding the pleiotropic activities of resveratrol and vitamin D, basic biological processes and mechanisms common to both resveratrol and vitamin D, and specific diseases and maladies controlled and/or ameliorated by resveratrol and vitamin D.

Resveratrol and vitamin D: basic background, understanding and relevance

The two immediately following subsections are devoted to separate discussions of resveratrol and vitamin D. They will provide the basic background and foundational understanding relevant to the hypothesis being presented here.

Resveratrol

The polyphenol resveratrol is present in many plants and fruits, including grape skins (and thus in red wine), peanuts and a large variety of berries, flowers and leaves. Resveratrol is an antimicrobial substance synthesized *de novo* to combat attack by pathogens such as bacteria or fungi and as such is an exemplary example of defense-promoting molecules called phytoalexins, a Greek word meaning "plant protector". (Although phytoalexins have long been inferred to be important in the defense of plants against fungal infections, few reports show that they provide human resistance to infections [1]). In their 1992 seminal article about the French Paradox (an appreciably lower incidence of coronary heart disease in France than in comparable countries), Renaud and de Lorgeril presented evidence that dietary fat and blood cholesterol may not be the determining factors for mortality and morbidly due to heart disease [2]. Cardioprotection was eventually attributed to red wine and its polyphenolic phytoalexin component resveratrol. However, the contribution of resveratrol vis-à-vis wine and/or alcohol per se to the French Paradox is still a matter of considerable debate [3], since a healthier pattern of drinking ("the pattern being more important than the content of the bottle" [4]) or more favorable risk traits in wine drinkers may be involved [5]. It has been stated that the totality of evidence suggests that the major beneficial component of alcoholic beverages on cardiovascular mortality is in fact ethanol per se rather than some other component [6], and that it is even likely that any apparent additional beneficial effect of wine on health in addition to that of ethanol itself is a consequence of confounding [7]. While the contribution of resveratrol to explain the French Paradox may still be debatable, there is ample preclinical evidence that resveratrol induces pleiotropic health benefits, including antioxidative, anti-inflammatory, anti-ageing, cardioprotective, anti-cancer, and neuroprotective [8]. Ca. year 2011, most if

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not all clinical trials of resveratrol have only studied its pharmacokinetic and metabolite profile in humans [9].

Vitamin D

Our understanding and appreciation of how vitamin D mediates biological responses have recently entered a new era. Historically, most interest in vitamin D had been relegated to its actions in calcium homeostasis and bone formation. However, over the past few decades new evidence has emerged from laboratory and human studies showing that vitamin D generates positive and important biological responses which it also shares with resveratrol: antioxidative, anti-inflammatory, anti-ageing, cardioprotective, and neuroprotective. Like resveratrol, vitamin D is involved in cell-cycle control, and thus of the disease process of cancer [10]. Reasons have also been advanced which strongly suggest that vitamin D provides protection against low-level radiation damage in general [11] and at high altitudes in particular [12], and against influenza pandemics [13] as well as exerting salutary control/amelioration of various maladies contributing to ageing [14].

For most individuals, casual sunlight exposure accounts for more than 90% of vitamin D in the body [15]. Whether obtained through ultraviolet radiation (UV) induced cutaneous production of cholecalciferol (vitamin D_3) or through dietary intake of cholecalciferol and/or ergocalciferol (vitamin D_2), vitamin D is essential for the adequate production of the physiologically active secosteroid hormone calcitriol, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), which has potent cell signaling activity and is tightly regulated at the tissue level. (Vitamin D_3 is more potent than vitamin D_2 in humans [16].) The main long-term actions of the hormonally active form of vitamin D are genomic effects mediated via the genomic pathway involving binding of the hormone to specific high-affinity intracellular vitamin D receptors (VDRs) present in essentially all tissues and cells in the body [17]. Calcitriol, the active metabolite of vitamin D, initiates the physiological responses of $\geqslant 36$ cell types that possess VDRs, with the number of detected target organs having increased 9-fold since the early 1970s [10]. Calcitriol activates VDRs to transcribe or repress up to 2000 different genes that control cell growth and other cellular functions [18]. The discussion on hormesis in this report will provide examples of how VDRs are also affected by resveratrol. The vitamin D intermediate metabolite 25-hydroxyvitamin D, 25(OH)D, the predominant form of vitamin D in the blood, is commonly used as the vitamin D exposure biomarker since it has been correlated with total exposure from both endogenous UV-induced production and the diet [19]. It is of crucial importance that preclinical, epidemiological and clinical studies of resveratrol should monitor serum 25(OH)D in order to gauge potential interactions between resveratrol and vitamin D.

Some biological processes and mechanisms common to both resveratrol and vitamin D: hormesis, oxidation (antioxidation and prooxidation), and programmed cell death (apoptosis and autophagy)

The immediately following subsections are devoted to discussion of three of the biological mechanisms and processes relevant to the hypothesis being presented here: hormesis, oxidation (antioxidation and prooxidation), and programmed cell death (apoptosis and autophagy). As will be developed, each of these mechanisms and processes can be triggered and controlled by resveratrol and vitamin D either alone or in concert. An integral and important part of the discussion will be the presentation of specific examples of the occurrences of these mutually shared processes in resveratrol and vitamin D. The shared commonality of these processes and mechanisms vis-à-vis both resveratrol and vitamin D lend credence and support to the hypothesis that significant interpretive problems can and do arise from the interactions and mutual effects of resveratrol and vitamin D.

Hormesis

Hormesis is the biological and toxicological concept that small quantities have opposite effects from large quantities. In the hormesis paradigm, agents induce dose–responses having two distinct phases (i.e., biphasic, non-monotonic) with biologically opposite effects at different doses. Hormesis challenges both the threshold and the linear, non-threshold (LNT) dose–response models which postulate only quantitative changes with dosage; but also, more importantly, hormesis suggests that as the dose changes, not only quantitative changes but also qualitative changes occur vis-à-vis control (background) and high doses [20]. Depending on endpoints measured, the dose–response can take different forms: J-, U-, or inverted U-shaped. Most commonly there is a stimulatory or beneficial effect at low doses and an inhibitory or toxic effect at higher doses. Evidence abounds for nutritional hormesis in general [21] and in ageing in particular [22]. The hormetic U-shaped dose–response between selenium status and human prostatic DNA damage has established the crucial importance of monitoring the detailed dose–response of one hormetic agent (in this particular case selenium) in determining and controlling outcome in humans (in this particular case prostate cancer) [23]. Life gets a lot more interesting (and most likely much more complicated!) when two (or even more) hormetic agents are simultaneously in play (perhaps acting synergistically, additively, or even at repressive cross-purposes). There are two hormetic agents being considered here: resveratrol and vitamin D. Therefore in light of the hypothesis being presented here (mutual interactions between resveratrol and vitamin D), it is of crucial importance to monitor doses of both resveratrol and vitamin D (via serum 25(OH)D levels). Both laboratory and human evidence for hormesis will now be reviewed and discussed for resveratrol and vitamin D, respectively.

A thorough and compelling review of the literature has revealed that resveratrol commonly displays hormesis with opposite effects occurring at low- vis-à-vis high-doses in a wide rage of biological models/systems affecting numerous endpoints of biomedical and therapeutic significance (tumor and non-tumor cell lines, human disease/injury including neurological maladies such as Alzheimer's disease, parasitic diseases, etc.) [24,25]. It is known from both human and laboratory studies that the cardioprotective effects of alcohol, wine and wine-derived resveratrol display a hormetic J-shaped dose–response [26,27] which for resveratrol has been explained as follows [28]. At lower doses, resveratrol acts an anti-apoptotic agent providing cardioprotection as evidenced by increased expression of cell survival proteins, improved post-ischemic ventricular recovery and reduction of myocardial infarct size and cardiomyocyte apoptosis, and by maintaining a stable redox environment compared to control. However, at higher doses resveratrol depresses cardiac function, increases myocardial infarct size as well as acts as a pro-apoptotic compound. Both pro- and anti-apoptosis will be discussed in detail later.

MCF-7, the most frequently studied human breast tumor cell line with respect to resveratrol, has commonly displayed resveratrol-induced biphasic dose–responses with resveratrol acting as an estrogen agonist at low concentrations and as an antagonist at higher concentrations [24]. There is evidence for hormesis in resveratrol-modulation of astroglial cells, which are key modulators of neuropathology events and evince extracellular glutamatergic system uptake. (As will be developed, both resveratrol and vitamin D exert control of the glutamatergic system.) In cortical astrocyte cultures, resveratrol increased glutamate uptake and glutathione

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(GHS) content at 25 μM concentration but decreased glutamate uptake at 250 μM concentration, indicating a hormetic phenomenon [29]. At low doses resveratrol stimulates angiogenesis (the physiological process involving the formation of new blood vessels from a preexisting vascular bed) which leads to cardioprotection, whereas at higher doses it evinces hormesis by blocking angiogenic response [30]. Resveratrol can behave as an antioxidant, yet it can induce redox signaling. At low concentrations resveratrol may act as an antioxidant by scavenging reactive oxygen species (ROS), whereas at higher doses it may evince hormesis by functioning as a prooxidant [30,31]. By these actions, resveratrol manifests quintessential hormesis: at lower doses it maintains cardiovascular, neuroprotective and general human health, whereas at higher dose by its pro-apoptotic and other actions it is detrimental to the cardiovascular and neural systems as well as to healthy cells (although conducive to killing tumor cells).

There is a great amount of evidence from both laboratory and human studies attesting to the fact that vitamin D also acts as a hormetic agent. Biphasic dose–responses abound in laboratory studies of the hormonally active form of vitamin D, $1,25(OH)_2D_3$: human hair follicle growth and fiber production [32], cultured rat hepatic Ito cells [33], and vascular smooth muscle cells [34]. For example, $1,25(OH)_2D_3$ can either stimulate or inhibit DNA synthesis as shown by its promotion of *in vitro* proliferation at low concentrations and inhibition at higher pharmacological doses of the human mouse keratinocytes, cells which synthesize and excrete the insoluble keratin that strengthens and waterproofs the skin's outer surface [35]. The many *in vitro* skin studies supporting vitamin D hormetic responses [36] have proven prescient for human studies, with vitamin D being reported to exemplify hormesis in humans by the fact that low doses have stimulatory effects promoting epidermal wound healing in contrast to high doses inhibiting psoriasis [37]. The role of vitamin D-induced hormetic effects in human ageing has also been discussed [14]. The importance of hormetic vitamin D effects in humans has been stated in the 2008 review by the International Agency for Research on Cancer where the need has been raised to further assess the potential for J- or U-shaped association between vitamin D status and risk of cancers of the prostate, pancreas, and esophagus [38]. U-shaped relationships between vitamin D status and cancer, as well as for cardiovascular risk and overall mortality (similar to relationships also described for iron, folic acid, selenium, and beta-carotene), have also been cited [39,40]; although some such associations have been critiqued [41].

In addition to reports of hormesis in either resveratrol or vitamin D, per se, a laboratory study has also reported hormetic responses involving tandem interactions between resveratrol and vitamin D receptors, with VDRs serving as resveratrol's molecular targets. In two estrogen receptor positive human breast cancer cell lines, MCF-7 and T47D, resveratrol affected hormetic dose–responses for both VDR promoter activity and cell proliferation, with even a triphasic dose–response for cell proliferation [42].

Oxidation: antioxidation and prooxidation

During the course of normal metabolism, free radical reactive oxygen species (ROS) are produced within the respiratory chain of mitochondria with the ability to oxidize and damage a variety of cellular constituents including lipids, amino acids, carbohydrates, DNA, and proteins. While free radicals are necessary to defend organisms against infective agents, high ROS cellular levels can damage many critical cellular components that might lead to a variety of clinical abnormalities including cardiovascular disease, diabetes, neurodegenerative disease, and cancer [43]. Free radicals are normally neutralized by efficient antioxidant enzymes with a large number of antioxidative agents having been shown to exhibit protective effects in cell culture and animal models [44]. But it should be noted that human antioxidant supplementation has pros and cons for any population that raises numerous questions, issues, and challenges [45]. In this regard it is important to note that low-ROS levels may be essential triggers and mediators of various protective mechanisms with excessive antioxidant levels threatening such protection. ROS-induced protective mechanisms include apoptosis and phagocytosis (which fights infectious microorganisms), as well as sundry detoxification reactions [46]. In further support and enlargement of previously noted resveratrol-induced oxidative hormesis, it has been generally proposed that low-level ROS induces hormetic effects and that it is only at high levels that ROS inflicts cell damage causing underlying disease processes [47].

Depending on the biological system, resveratrol can scavenge the superoxide anion (O_2^-) as well as hydroxyl radicals although at a slower rate than that of ascorbic acid. While resveratrol does not function as a strong *in vitro* scavenger of ROS, it does function as a potent *in vivo* antioxidant which probably arises from its ability to increase nitric oxide (NO) synthesis, which in turn acts as an antioxidant. There have been many laboratory reports of vitamin D_3 exerting protective antioxidative actions [48]. An *in vitro* study reported that vitamin D_3 not only suppressed autooxidation but may also be one of the most powerful antioxidants in biological organisms based on the fact that it was some 10^3 more potent than a water soluble vitamin E analog in inhibiting zinc-induced central nervous system (CNS) oxidative stress [49]. Interestingly, the active metabolite of vitamin D, $1,25(OH)_2D_3$ has been reported to protect some nonmalignant human prostate epithelial cell lines, but not some malignant human prostate epithelial cells from oxidative stress-induced cell death [50].

There is a wealth of evidence attesting to the facts that both resveratrol [51,52] and vitamin D [48,53] exert control of the glutamatergic system which by maintaining antioxidant enzymes plays a key role in cellular defense against free radical damage. Their actions in combating neurodegenerative diseases and cancer through their control of the antioxidative glutamatergic system will be developed later in this report. It should also be noted that both resveratrol and vitamin D may equally well serve as a hormetic agent triggered by ROS. As already noted, at low concentrations resveratrol by scavenging ROS may act as an antioxidant, whereas at higher doses it may evince hormesis by behaving as a prooxidant [30,31,54]. Vitamin D may equally well serve as a hormetic agent triggered by low-level ROS. The vitamin D-mediated hormetic agency could be programmed cell death (apoptosis and/or autophagy), or any of the other mechanisms discussed in this report.

Programmed cell death: apoptosis and autophagy

There are at least two types of programmed cell death (PCD): apoptosis and autophagy. Apoptosis is defined by a variety of distinct morphological changes mediated by a family of cysteine proteases (caspases) and a number of other regulatory proteins which enhance the elimination of various damaged and dysfunctional cells presumably caused by oxidative stress, glycation and DNA damage [55]. Autophagy (in Greek, "to eat oneself") is an intracellular event in which a cell digests its own constituents. Autophagy disposes of defective organelles and macromolecular structures as well as cytosolic components such as damaged and aggregate-prone proteins by engulfing cytoplasmic constituents with a double-membrane vacuole, the autophagasome [56]. Autophagy depends on autophagy proteins and as a process of self-consumption has earned the sobriquet "garbage disposal mechanism" [57]. The hallmarks of apoptotic cell deaths are membrane blebbing, chromatin condensation, and fragmentation of the nucleus and the cytoplasm into apoptotic bodies; while autophagic cell death is characterized by cell shrinkage and the formation of multiple

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autophagic vacuoles [58]. Paradoxically, depending on circumstances, both apoptosis and autophagy may be involved in both health and disease progression. Because of their paradoxical and controversial involvements in both cell survival and cell death, apoptosis and autophagy (either independently or together in concert) have been identified as double-edged swords [59] as well as being a Dr. Jekyll and Mr. Hyde phenomenon [60].

Both resveratrol and vitamin D have been shown to influence the regulation of genes and protein products that promote active apoptotic death, for example in numerous (but not all) normal and cancer cell types [14,61]. As already noted in the discussion of antioxidants, reactive oxygen species may be essential biochemical intermediates in the progress of apoptosis [62], with apoptosis being triggered or blocked depending on the severity of oxidative stress [63]. Among the genes and proteins implicated in the regulation of apoptosis are the p53 as well as other tumor suppressor genes, the tumor necrosis factor α (TNF-α), the transcription nuclear factor kappa B (NF-κB), and the B cell lymphoma-2 (beclin-2) family of proteins. The p53 gene regulates the intracellular redox state and induces apoptosis by a signaling pathway dependent on ROS production [64]. (p53 is important not only for its involvement in apoptosis, but also in DNA repair, senescence, cell cycle arrest, and anti-tumor activity with more than 50% of human cancers associated with one or more of its mutations [65].) The beclin-2 protein family consists of both anti-apoptotic, pro-survival proteins such as bcl-2 and bcl-X_L (B cell lymphoma extra large) that confer resistance to active cell death by a number of stimuli [66]; as well as pro-apoptotic, anti-survival proteins such as bax (bcl-2 associated X protein), bak (bcl-2 antagonist killer), and bad (bcl-2 associated death promoter) [67]. As an example of the complex interactions involved with vitamin D alone, vitamin D upregulates the p53 apoptotic regulator gene in concert with decreased expression of the anti-apoptotic beclin-2 proteins, bcl-2 and bcl-X_L [68]. Resveratrol likewise exerts control over these same molecular targets: p53, TNF-α, and the bcl-2 protein family [1,69].

Both resveratrol and vitamin D have been shown to stimulate autophagy vacuolization, although for tumors it is often difficult to determine whether the response is pro-tumorigenic or anti-tumorigenic [70]. Among the common molecular targets shared by both resveratrol and vitamin D are bcl-1 and bcl-2. For example, a study showed that a vitamin D analog induced massive autophagic cell death via a pathway involving bcl-1 acting as an autophagic-inducing tumor suppressor gene important in human tumor suppression [71]. Autophagic cell death has been related to free cystolic calcium ($[Ca^{2+}]_c$) induced by vitamin D compounds in a beclin-2 family regulated fashion [72]. The earlier report [73] that vitamin D compounds induced autophagy and apoptosis in MCF-7 cancer cells has been explained by the nature of the calcium ion itself [74].

Mutual control and/or amelioration of specific diseases and maladies by resveratrol and vitamin D

The immediately following subsections are devoted to discussion of three specific diseases and maladies: neurodegenerative diseases, cardiovascular diseases and cancer. As will be developed, each of these maladies and diseases can be separately controlled and/or ameliorated by resveratrol and vitamin D. An integral part of the discussion will be the presentation of evidence that resveratrol and vitamin D also have mutual multiple targets and molecular signaling pathways. The commonality of diseases and maladies controlled and ameliorated by resveratrol and vitamin D and the mutual molecular targets and signaling pathways shared by resveratrol and vitamin D lend credence and support to the hypothesis that significant interpretive problems arise from the interactions and common mutual effects of resveratrol and vitamin D.

Neurodegenerative diseases

Neurodegenerative disorders are among the numerous degenerative processes in which resveratrol and several of its derivatives prevent or directly interfere with. The CNS is a target of resveratrol, which can pass the blood–brain barrier and induce neuroprotective effects through its direct antioxidant and scavenger effects, its ability to modulate and improve cellular antioxidant defenses, and through gene transcription regulation [75]. Numerous *in vitro* and *in vivo* studies have shown that resveratrol and several of its derivatives demonstrate very promising anti-neurodegenerative properties [76] and specific activities that can delay or alter the progression of such neurodegenerative disorders as brain ischemia, stroke, and Huntington's, Parkinson's and Alzheimer's diseases [77]. Different mechanisms, including antioxidation and gene transcription-regulation, have been suggested to be involved in the neuroprotective actions of resveratrol [76].

As already noted, vitamin D appears to play an important role in autophagy whose disturbance contributes to the pathogenesis of neurodegenerative disorders such as Amyotrophic Sclerosis and Parkinson's, Huntington's and Alzheimer's diseases [78]. Autophagy has been cited as a protective mechanism against neurodegenerative disorders by enhancing the clearance of mutant aggregate-prone proteins [79,80]. Vitamin D receptors (VDRs) have been located in multiple brain regions affected by neurodegenerative disease, including the hippocampus and basal forebrain [81]. There is growing evidence that the hormonally active form of vitamin D may combat neurodegenerative as well as neuroimmune disorders by its important role in the central nervous and immune systems and in its promotion of neuronal cell survival [82]. Indeed, $1,25(OH)_2D_3$ has been shown *in vitro* to diminish neuronal damage related to ageing, ischemic brain injury, seizures, and elevated levels of transition metals [49,83,84], and to attenuate neuronal cell damage evoked by a plethora of toxic agents [85,86]. Evidence from observational and laboratory studies supporting the hypothesis that vitamin D can reduce the risk of developing dementia has been reviewed [87]. The observational evidence includes the fact that low serum 25(OH)D levels are associated with increased risk of cardiovascular periodontal diseases, diabetes mellitus, depression, dental caries, and osteoporosis – all of which are either considered risk factors for dementia or have preceded incidence of dementia, while the laboratory evidence includes findings on the role of vitamin D in neuroprotection and inflammation reduction.

Glutamate, a salt of glutamic acid, is a key molecule in cellular metabolism. In neuroscience, glutamate is the major excitatory neurotransmitter in the CNS that is important for learning and memory and plays a key role in long-term potentiation (the long-lasting signal transmission enhancement between two neurons resulting from synchronous stimulation). Glutamate also plays an important role in neural plasticity and neurotoxicity and for maintaining glutathione (GHS), the intracellular free radical scavenger which is the main antioxidant defense of the brain. A large variety of neurological and psychiatric disorders, including depression, anxiety disorders, schizophrenia, chronic pain, epilepsy, as well as Alzheimer's and Parkinson's diseases, demonstrate pathophysiology impairments in the glutamatergic system [88]. There is substantial evidence that both vitamin D and resveratrol exert important influence and control of the glutamatergic system. Hormonally active vitamin D through its antioxidant action has been shown to enhance intracellular GSH concentration and to protect against reactive species in the CNS [89,90]. *In vitro* studies have shown that resveratrol is able to induce significant increases in glutamate uptake, glutamine synthetase (GS) activity and GHS levels. These resveratrol-induced increases have been offered as an explanation for resveratrol's efficacy in protecting against brain disorders such as Alzheimer's and Parkinson's diseases, stroke and

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ischemia injury, and have thereby been proposed to represent an important pharmacological opportunity [91].

Cardiovascular diseases

Resveratrol appears to promote cardiovascular health in numerous ways, especially through its antioxidative control of various redox signaling mechanisms. At lower doses, resveratrol-mediated survival of cardiac myoblasts is in part mediated through the induction of autophagy, which along with other enhanced survival signals helps to recover the cells from injury [92,93]. Resveratrol decreases low-density lipoprotein (LDL) cholesterol levels, increases high-density lipoprotein (HDL) cholesterol levels, induces vasorelaxation presumably through induction of nitric oxide (NO) synthesis, inhibits the potent vasoconstrictor endothelin (ET), reduces ventricular arrhythmias, possesses anti-platelet and anti-thrombin activities (aspirin-like effects), inhibits formation of soluble adhesion molecules, reduces blood pressure, ameliorates ischemic reperfusion injury, regenerates the infracted myocardium, and at low levels can significantly inhibit intracellular and extracellular ROS production by enhancing the intracellular free radical scavenger glutathione (GHS) which as already been noted is the brain's main antioxidant defense [3,94]. As already noted, resveratrol also modifies angiogenesis. At low doses it is pro-angiogenic, providing cardioprotection [30], and its hormetic properties have also already been noted.

There is evidence that inadequate vitamin D status and living at higher latitudes with concomitant inadequate vitamin D status may contribute to the pathogenesis and progression of cardiovascular disease. Serum 25-hydroxyvitamin D levels vary with season, latitude, geography, and altitude. Interestingly, the risk of cardiovascular disease is noted to be highest in areas of increased geographic latitude and during winter months, which parallels the trend where serum 25(OH)D levels are the lowest [95]. The renin-angiotensin system plays a central role in the regulation of blood pressure, electrolyte, and volume homeostasis. Knockout mice studies confirm that the absence of vitamin D receptor activation leads to upregulation of the renin-angiotensin system with the development of hypertension and left ventricular hypertrophy [96,97]. Clinical studies have reported cross-sectional associations between lower vitamin D levels and hypertension, coronary artery calcification, and prevalent cardiovascular disease [98,99], and with stroke [100], peripheral artery disease [101,102], and congestive heart failure [103,104]. Vitamin D improves muscular function, controls blood pressure, and improves glucose tolerance; all of which are underlying causes of congestive heart failure [105]. Vitamin D's actions in controlling cytokine immune system signaling molecules assume importance in cardiology through its anti-inflammatory actions. Elevated circulating concentrations of pro-inflammatory cytokines may contribute to the pathogenesis of congestive heart failure with *in vitro* studies showing that vitamin D suppresses pro-inflammatory cytokines and increases anti-inflammatory cytokines [106,107].

Some evidence for vitamin D and resveratrol mutually sharing the same cardiovascular signaling pathways and molecular targets will now be presented. Vitamin D receptors are distributed in the vascular smooth muscle, endothelium, and cardiomyocytes. *In vitro*, both the hormonally active form of vitamin D and resveratrol regulate the growth and proliferation of vascular smooth muscle and endothelial cells [108,109]. As already noted, hormetic biphasic dose–responses have been shown in $1,25(OH)_2D_3$ laboratory studies of vascular smooth muscle cells [34]. In both laboratory rodents and humans, there is an age-related upregulation of pro-inflammatory cytokine tumor necrosis factor alpha, TNF-α, and that disruption of TNF-α signaling confers vascular protection in ageing [110]. A double-blind, randomized, placebo-controlled trial of daily vitamin D supplementation in congestive heart patients has been found to affect immune-modulating cytokines in desirable ways by preventing increases in serum concentrations of TNF-α [111]. Such changes indicate that vitamin D has protective effects on the heart and the atherosclerosis that precipitates congestive heart failure and serves as an anti-inflammatory agent for the treatment of this disease as well as other diseases associated with upregulated pro-inflammatory cytokines. Resveratrol has likewise been found to downregulate vascular and cardiac expression of TNF-α in both *in vivo* and *in vitro* vasculature studies [112,113]. Both vitamin D and resveratrol mediate some of their effects by exerting control over redox-sensitive NF-κB, a ubiquitously expressed transcription factor that regulates over 500 genes [69] and which plays a critical cardiovascular role through endothelial activation and inflammation control [114,115]. Resveratrol's cardioprotective effects in mice have been ascribed to its control of TNF-α-induced NF-κB signaling pathway activation [116]. Vascular endothelial growth factor (VEGF) proteins are intimately involved in angiogenesis. Vitamin D is involved in angiogenic cardiovascular activity through VEGF proteins, e.g., $1,25(OH)_2D_3$ has been found to control vascular smooth muscle cells through a VEGF-mediated pathway [117]. Resveratrol is likewise involved in angiogenic activity, e.g., it has been found to suppress the growth of new blood vessels in animals by directly inhibiting capillary endothelial cell growth by blocking VEGF receptor-mediated angiogenic responses [118].

Cancer

A number of preclinical findings suggest resveratrol to be a promising natural weapon against cancer, imparting chemopreventive as well as therapeutic responses (although, ca. 2007, no results of human clinical cancer trials had been reported) [8,119]. Laboratory studies have shown that resveratrol affects all three discrete stages of carcinogenesis (initiation, promotion, and progression) by modulating cell-signaling molecules that regulate cell division and growth, programmed cell death, inflammation, invasion, metastasis, and angiogenesis of tumor cells [8,69]. *In vitro* studies indicating that resveratrol inhibits proliferation of a wide variety of human cancer cells have led to numerous preclinical animal studies to evaluate resveratrol's potential for cancer chemoprevention and chemotherapy. In general, resveratrol's anticancer activity has been attributed to cell antiproliferation/antiprogression and induction of programmed cell death [1].

Vitamin D also regulates the cell cycle and cell proliferation and by its actions in preventing unscheduled or aberrant proliferation has earned the sobriquet "guardians of the cell cycle" [120]. Treatment of cell types with vitamin D_3 has been found to cause an arrest of cell cycle progression in the G_0–G_1 phase resulting in decreased number of cells in the S phase [121]. Vitamin D also upregulates the genes which control the p53 as well as other tumor suppressor proteins which contribute to cell cycle arrest as well as to programmed cell death and DNA repair after genotoxic or non-genotoxic stresses [122].

Both resveratrol and vitamin D regulate such important cell-signaling molecules as NF-κB, Akt (a kinase that regulates cell survival signals), MAPF (mitogen-activated protein kinase), Fas antigen receptors, TNF-α, bcl-2, bcl-xL, and p53; all of which regulate cell survival or programmed cell death in pre-cancerous or cancer cells without in many instances adversely modulating the activity of normal cells [8,14]. Available reports suggest that the anticarcinogenic effects of resveratrol may be mediated by the induction of glutathione (GHS) because this endogenous tripeptide molecule can detoxify various carcinogens, serve as an intracellular antioxidant, and also regulate DNA and protein synthesis [123]. As already noted, there is substantial evidence that both vitamin D and

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resveratrol exert substantial influence and control of GHS. Both resveratrol and vitamin D regulate the enzyme superoxide dismutase (SOD) which plays an important anti-cancer role in acting against free radical damage [1,53,124]. Caspase-3, a common downstream effector of multiple apoptotic signaling pathways in cancer studies, can be downregulated by vitamin D [125] and upregulated by resveratrol [126]. Both resveratrol and vitamin D activate the protein kinase C (PKC) which appears to participate in signaling pathways involved in cell proliferation, differentiation, apoptosis, and malignant transformation [127–129]. Animal laboratory studies have also shown that both resveratrol and vitamin D control cancer by suppressing angiogenesis of tumor cells by directly inhibiting capillary endothelial cell growth by blocking both vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) receptor-mediated angiogenic responses [118,130,131]. In addition, there is laboratory evidence for hormetic responses (U- and inverted U-shaped dose–response curves) for anti-angiogenic cancer-control agents which target the VEGF signaling pathways [132].

Discussion and conclusions

The biological processes undergirding the pleiotropic activities of resveratrol and vitamin D have been presented. The basic biochemical processes and mechanisms common to both resveratrol and vitamin D have been considered. Specific diseases controlled and/or ameliorated by both resveratrol and vitamin have been discussed. These facts have laid the basis and buttressed the hypothesis being offered here: resveratrol and vitamin D have important mutual processes, interactions and induced effects that could seriously affect the interpretation of their preclinical, epidemiological and clinical studies. The hypothesis has important ramifications especially in light of the many ongoing efforts to understand the role of resveratrol in the human condition. The interpretation of preclinical, epidemiological and clinical studies of resveratrol may be seriously compromised if the oftentimes dual and/or contrary effects of vitamin D vis-à-vis resveratrol are not taken into account. It is proposed that resveratrol studies should also establish serum 25(OH) levels in order to quantitatively take into account the possibility of important interactions between resveratrol and vitamin D.

Conflict of interest statement

The author has no financial and personal relationships with other people or organizations that could inappropriately influence (bias) his work.

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