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ORIGINAL ARTICLE

Natural antioxidants in prevention of accelerated ageing: a departure from conventional paradigms required

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Abstract

The modern lifestyle is characterised by various factors that cause accelerating ageing by the upregulation of oxidative stress and inflammation—two processes that are inextricably linked in an endless circle of self-propagation. Inflammation in particular is commonly accepted as aetiological factor in many chronic disease states, such as obesity, diabetes and depression. In terms of disease prevention or treatment, interventions aimed at changing dietary and/or exercise habits have had limited success in practise, mostly due to poor long-term compliance. Furthermore, other primary stimuli responsible for eliciting an oxidative stress or inflammatory response—e.g. psychological stress and anxiety—cannot always be easily addressed. Thus, preventive medicine aimed at countering the oxidative stress and/or inflammatory responses has become of interest. Especially in developing countries, such as South Africa, the option of development of effective strategies from plants warrants further investigation. A brief overview of the most relevant and promising South African plants which have been identified in the context of inflammation, oxidative stress and chronic disease is provided here. In addition, and more specifically, our group and others have shown considerable beneficial effects across many models, after treatment with products derived from grapes. Of particular interest, specific cellular mechanisms have been identified as therapeutic targets of grape-derived polyphenols in the context of inflammation and oxidative stress. The depth of these studies afforded some additional insights, related to methodological considerations pertaining to animal vs. human models in natural product research, which may address the current tendency for generally poor translation of positive animal model results into human in vivo models. The importance of considering individual data vs. group averages in this context is highlighted.

Keywords Inflammation · Neutrophil · Pre-clinical · Translation · Rodent to human · Chronic disease

Introduction

While the comforts of the modern lifestyle are certainly much desired, it comes at a premium. Modern man (and woman) is finding it increasingly challenging to keep up with the Olympic-level balancing act between work performance, health, family commitments, social interaction, etc. As a result, as often blamed and shamed in the literature, modern man adopts a high-psychological stress, sedentary lifestyle with high fast food and/or sugar intake, all of which contribute to the development of lifestyle-associated conditions such as depression, obesity, type II diabetes, and cardiovascular disease [16, 19]. In addition to those named above, other factors—such as pollution [41], poor body posture [11, 70] and lack of sleep [45]—may further contribute to metabolic maladaptation, in particular by increasing oxidative stress-associated allostatic load.

In terms of mechanisms involved, a parallel can be drawn between maladaptive consequences of the modern lifestyle and old age. Lifestyle-associated conditions and old age are both characterised by relative glucocorticoid insensitivity and lower glucocorticoid receptor levels, a decreased resistance to infection, increased levels of oxidative stress and an increasingly pro-inflammatory phenotype. This suggests that many modern chronic conditions are the result of maladaptation that accelerates the ageing process (Fig. 1). Evidence of this is already becoming evident, in particular in developing countries where urbanisation is occurring at an ever-escalating rate. For example, a study in 266 South African university students reported that 4% of students in their early twenties already

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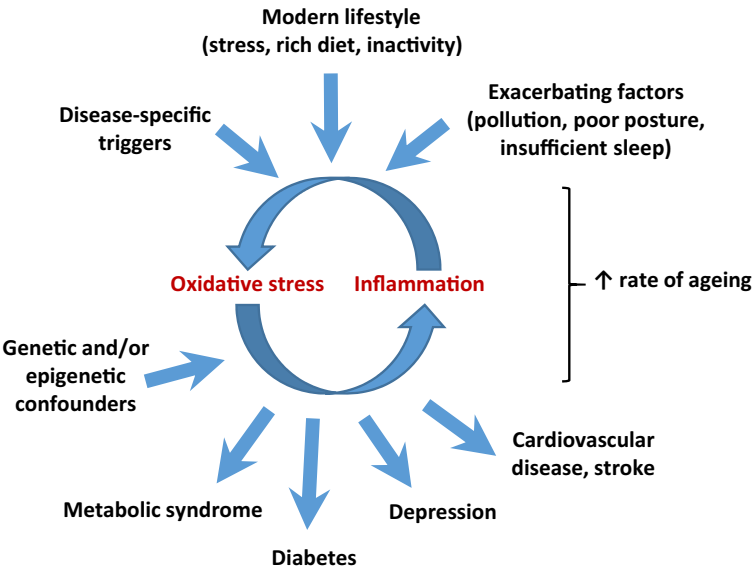

Fig. 1 Accelerated ageing, brought about by a chronic inflammation-oxidative stress loop, contributes to the development of chronic disease

fulfilled the International Diabetes Federation (IDF) diagnostic criteria for the metabolic syndrome, a disease usually associated with more advanced age. In this cohort, ≈15% of students exhibited central obesity, while ≈35% displayed increased resting triglyceride levels [59]. Interestingly, in a follow-up study, these maladaptations seemed to display gender differences, with poor dietary habits in males named as main culprit, while in females, high psychological stress levels seemed to play a relatively bigger role [60]. Even in developed countries such as the United States of America (USA), alarming increases in the incidence of "conditions of the middle-aged" (obesity, diabetes, stroke, lipid disorders) were reported in individuals within their first three decades of life [20]. Furthermore, in terms of obesity specifically, epigenetic studies (e.g. [66]) suggest that lifestyle-associated physiological maladaptations may be epigenetically transferred both maternally and paternally, to negatively affect future generations as well. Together, these studies highlight the importance of disease prevention starting already in relatively young individuals.

Targets for prevention of accelerating ageing

In addition to disease-specific aetiological factors, the main maladaptive processes implicated in the context of accelerated ageing are oxidative stress and inflammation. As recently reviewed [50], once upregulated, these processes deplete the body's natural antioxidant defences, resulting in a self-propagating cycle of cell damage and repair. As result of this constantly upregulated cell renewal, the rate of physiological ageing exceeds chronological ageing, as evidenced by a relatively faster shortening of telomere length [22, 74] and decrease in sirtuin-1 levels [55]. Sirtuin-1 is also implicated in the regulation of apoptosis by deacetylation of p53 to inhibit p53-dependent transcription in models of cellular stress [51], which further implicates its importance as indicator of accelerated ageing in the context of chronic disease.

Accelerated ageing and the involvement of oxidative stress and inflammation are not new concepts. In terms of obesity in particular, a decreased adiponectin level and increased immune cell infiltration into adipose tissue is known to result in increased secretion of pro-inflammatory cytokines such as macrophage chemotactic protein-1 (MCP-1), interleukin-6 (IL-6) tumour necrosis factor-alpha (TNF-α) and hypoxia inducible factor-1 (HIF-1) [47]. Furthermore, excessive nutrient intake and obesity have been linked to increased oxidative stress in adipose tissue, which in turn results in DNA damage and telomere dysfunction, leading to inflammation that exacerbates insulin resistance and leads to the development of type II diabetes via a p53-dependent pathway [40].

In addition, both type II diabetes and ageing are characterised by neurodegenerative processes. Molecular pathways commonly implicated in diabetes-associated neurodegeneration include cerebrovascular changes, non-enzymatic protein glycation, oxidative stress and alterations in neuronal calcium homeostasis [10]. Interestingly, the advanced glycation endproducts (AGEs) formed by non-enzymatic protein glycation is known to cause neurodegeneration via production of reactive oxygen species [72], cerebrovascular changes have a component of vascular damage which is linked to oxidative stress [54] and calcium influx in neurons are directly linked to oxidative stress [39]. Together, the literature clearly indicates the central role of oxidative stress in particular, in the development of diabetes and detrimental diabetes-associated long-term outcomes such as neurodegeneration. In the niche of preventive medicine, targeting of oxidative stress and inflammation is clearly a priority.

Prevention strategies involving plant products

Although many professionals in the health arena have been advocating healthier dietary habits and the benefits of habitual mild exercise to prevent chronic disease, clearly compliance on these fronts is poor. More recently, the focus of preventive practices have shifted towards the use of dietary supplements in an attempt to counter modern-living-associated damage.

Very recently for example, herbal remedies have been named as potential strategy for prevention of AGE accumulation, via its prevention of oxidative stress and beneficial effect on glycemic control [25]. In line with this, a South African product, which is globally consumed as tea—*Aspalathus linearis* (family *Fabaceae*), or Rooibos—has been shown to have potent antioxidant function [49], with proven antioxidant effectiveness in rodent models of cancer and diabetes [5, 75], as well as humans at risk of cardiovascular disease [38]. Also in the absence of specific illness, Rooibos supplementation was associated with beneficial effects on adrenal steroidogenesis and antioxidant status in humans, providing proof of its potential in the context of stress management and prevention of metabolic disorders [56]. In addition, Rooibos has been shown to ameliorate both high-glucose-induced inflammation [28] and dietary-induced metabolic disturbances in hyperlipidemic mice [6], suggesting further benefit in the context of obesity and diabetes. The widely demonstrated anti-inflammatory effects of Rooibos across various cells, animal and human models [28, 29, 31, 36, 56, 69] further stress the importance of this natural product as dietary supplement in the context of chronic disease.

Sceletium tortuosum (family *Aizoaceae*), which is anecdotally used to relieve pain and anxiety, is also increasing in popularity globally. Although not directly linked to obesity or diabetes, this plant has beneficial effects in the context of aetiological factors of these conditions, such as stress and anxiety [12, 34, 58]. These benefits may be ascribed to its ability to increase synaptic serotonin availability [15], as well as its beneficial effects on glucocorticoid and aldosterone production [68] as well as its neuroprotective effect achieved via modulation of specific neural enzymes [8, 15]. Furthermore, *Sceletium* extracts have demonstrated anti-inflammatory and antioxidant effects both in the central and peripheral compartments [7, 8], which also supports a role for this natural product not only in the prevention of chronic neurodegenerative diseases such as Alzheimer's disease, but also other chronic conditions resulting from the modern lifestyle.

On a note of caution, research has shown that not all products with known anecdotal benefit are suitable for application outside of the traditional, indigenous use context. For example, a South African succulent that has made global headlines for its appetite suppressant effects is *Hoodia gordonii* (family *Apocynaceae*). The interest in this plant originally stemmed from its use by the indigenous San Bushmen, to prevent hunger while hunting, which entailed following wounded animals for days without access to food. Although initial research confirmed this effect, a more recent rat supplementation study illustrated that the weight loss commonly reported after Hoodia consumption was ascribed to not only loss of fat, but also loss of muscle mass [62] While this undesired effect on muscle mass probably does not reach significance in a highly active population such as the San, it may have huge negative impact in an obese, sedentary population. Furthermore, a review on the topic [63] illustrated that the appetite suppression may be the result of delayed stomach emptying, resulting in distended stomachs (especially when consumers continue eating meals) which caused bloating and even adverse cardiovascular effects, making this plant a high-risk option for the management of obesity or diabetes.

Similarly, a large body of evidence exists in support of antioxidant [23, 71], anti-inflammatory [32, 76, 77] and anti-diabetic [35] actions of *Sutherlandia frutescens*, a legume indigenous to South Africa, which also has proven anti-stress efficacy [52, 57, 61, 64]. However, as many natural product extracts are in essence a cocktail of ingredients, its use in the context of chronic disease is complicated by the risk of drug interactions. Sutherlandia in particular, for example, has been implicated in exacerbation of HIV-associated neuroinflammation [1] and reduced (HIV) antiretroviral efficacy [42]. These examples illustrate that indigenous knowledge may in some cases be highly population- and/or context-specific. Therefore, comprehensive research and rigorous clinical assessment are required for natural products, as is the norm for conventional pharmaceuticals, in order to reduce the risk of unanticipated adverse effects.

That said, natural product research has made substantial advances over the past few years, addressing the need for not only scientific proof of anecdotal claims, but also for in depth, comprehensive research to elucidate in detail the mechanisms of action and specific therapeutic targets of natural products. One of the most widely researched plant products globally, is *Vitis vinifera* (grapes), which to date has been the topic of more than 8000 papers currently listed on PubMed. Uniquely, after relatively comprehensive investigations into this plant product, to our knowledge no negative data has been reported, identifying extracts from grapes as an important candidate in the chronic disease prevention niche. In the next section, we provide an overview of the most relevant benefits reported for extracts from this plant. At the same time, we address inadequacies of current paradigms that limit the progress of natural medicine research.

Grapes—a "pre-clinical" success story

Grapes contain a plethora of constituents with antioxidant capacity (e.g. flavonoids, phenolic acids and stilbenes). A

large body of evidence exists in support of beneficial effects of specific components from grapes, such as quercetin, catechin, anthocyanin, gallic acid and epicatechin.

Resveratrol—3,5,4′-trihydroxy-trans-stilbene, a non-flavonoid polyphenol present in high quantities in grapes—has arguably been most comprehensively assessed in the context of chronic disease. Both the anti-obesity mechanisms by which resveratrol prevents fat accumulation, as well as its antioxidant/anti-inflammatory properties, were reviewed very recently [9, 17, 18], so are not reviewed in detail here. However, a fact perhaps noteworthy to highlight in the context of accelerated ageing and diabetes specifically is that resveratrol has been reported to increase sirtuin-1 levels in rat adipose tissue [3]. As sirtuin-1 is known to inhibit the action of p53, this suggests a preventive effect in the aetiological pathway of type II diabetes in overweight individuals, which was mentioned earlier. However, as recently reviewed, while animal studies on resveratrol has been overwhelmingly positive, results from human studies are much less impressive, with little or no benefit reported [18].

This lack of support from human models is not unique to resveratrol. The catechin—a flavonoid-related group of compound also contained in grapes—also has a long history of benefit in the context of preventive medicine. For example, catechins with a gallocatechin moiety or a galloyl residue were reported to act as AMP-activated protein kinase (AMPK) activators in cellular models and in mice [43]. AMPK has recently emerged as an attractive target for the treatment of metabolic diseases, as recently reviewed [48], and upregulation of AMPK signalling is known to have benefit in the context of ageing-related neurodegeneration [21], again supporting preventive potential for a grape product in the context of chronic disease and accelerated ageing. Also, another catechin, epigallocatechin-3-gallate (which is also abundantly present in green tea), has been reported in cell culture and rodents to significantly inhibited the enzyme activity of both inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) [14], thereby reducing nitric oxide-associated oxidative stress. However, as recently stated in a review on the anti-obesity effects of catechins [67], data from human in vivo studies again fail to support the pre-clinical data.

Similarly, antioxidant and indirect anti-inflammatory function of another polyphenol group contained in grapes—the anthocyanins—have been well described in pharmacological studies [13, 30]. Also in pre-clinical biological systems, promising results have been reported. For example, our group has demonstrated grape extracts containing mainly anthocyanidins (anthocyanins are often deglycosylated to increase bioavailability of supplements, as they are more readily absorbed than the polyphenol glycosides [37], although they require stabilisation in this form) to increase oxygen radical scavenging capacity (ORAC) both in circulation and at tissue (skeletal muscle) level in rodents [44]. The extract showed efficacy both in preventive [27, 44] and therapeutic applications [26] in the context of rodent muscle contusion injury, where it limited neutrophil infiltration into damaged tissue, thereby minimising the inflammation-associated secondary (oxidative stress) damage. This in turn led to a faster pro- to anti-inflammatory phenotype switch in macrophages and faster tissue regeneration. These benefits also extended to HIV protein-associated neuroinflammation in a simulated blood brain-barrier, where human monocytic infiltration across the BBB in response to the chemotactic signal provided by HIV proteins was significantly attenuated after pre-treatment of the system with grape seed extract [2]. Furthermore, ageing-associated detriments in neutrophil chemokinetic movement were shown to be corrected after in vitro grape seed extract treatment of donated human neutrophils [50]. Taken together, the large body of evidence generated from pharmacological, cell culture and animal models points toward various products contained in grapes as having antioxidant, anti-inflammatory and anti-ageing application. Thus, the key to prevention of the maladaptations known to be central to accelerated ageing and chronic disease aetiology may be locked up in this fruit which is available in large quantities globally.

Achieving the seemingly impossible: positive human clinical data

However, despite the overwhelmingly positive results briefly outlined above, translation of pre-clinical data to clinical evidence in in vivo human models has proven to be more problematic. Several factors may contribute to this translation failure, for example differences in bioavailable dose due to differences in metabolic rate between species or differences in slightly different formulations of any particular compound, or different durations of treatment protocols employed. Through a series of studies by our group, using the exact same compound, and adjusting for species differences in metabolic rate, we are able to shed some light on this problem.

Firstly, as stated above, we have been able to demonstrate significant benefits with a particular grape-derived polyphenol in terms of antioxidant capacity (ORAC) and anti-inflammatory effect in a rat model, both in tissue and in circulation [26, 44], using both acute and chronic treatment. This effectively removes treatment duration as potential confounder in this particular case. We followed on from these studies with a clinical study in normally active, healthy individuals in their twenties, where subjects were supplemented with 140 mg anthocyanidins daily for a period of 2 weeks, with comprehensive assessment of inflammatory status before and after treatment [65]. The treatment dose used in this clinical trial was identical to those used in rat studies showing beneficial effects for the same product, but with adjustment for

differences in metabolic rate [53]. Similarly, the age (relative to total lifespan) of humans and rodents was comparable [4], eliminating these confounders as well. Sample size was restricted to $n = 10$ per treatment group. Although a similar sample size is sufficient to clearly indicate intervention benefits in similar parameters when using rodent models, in humans, inter- and intra-individual variations were relatively larger, potentially masking some subtle modulations to the system investigated, so that no main anti-inflammatory effects of the treatment intervention was evident after basic ANOVA analysis.

Although somewhat disheartening, given the care taken to exclude potential confounders as far as possible, this type of human study may provide much insight on the research approach required to increase "sensitivity" of studies using human models. For example, in Fig. 2, cumulative data from our database are presented to illustrate the difference in normal variability of just one indicator of antioxidant capacity (ORAC) in rodents vs. humans—even in the absence of any intervention. This illustrates how in the hands of the same laboratory staff, the data obtained from animal samples (all male Wistar rats) are much less variable than those from humans (a homogenous group of healthy, fit, young, male athletes). For the latter group, the obvious confounders such as supplement use, age, poor diet and sedentary habits—which could increase variability—do not apply here due to subject recruitment criteria employed. However, smaller variations in lifestyle habits, as well as psychological confounders, are usually much more difficult to control, resulting in the relatively larger inter-individual variability seen. In addition, it is important to acknowledge that natural compounds present in the normal diet of either rats or humans—but perhaps not both—may have synergism or antagonism with the test compound, resulting in species differences in effect of the treatment. This potential confounder is much more difficult to address, as a comprehensive comparison of rodent vs human nutrient consumption is required before we can even begin to make progress in this regard.

Furthermore, while experimental animals are housed in a sterile, highly controlled environment where minimal challenge to homeostasis should occur, it is near impossible to control the exposure of human subjects to a variety of oxidative and inflammatory stressors. This of course contributes not only to inter-individual, but also intra-individual variability, which further impacts negatively on the statistical power of clinical studies. Thus, a far smaller effect size of any treatment would be detectable in a rat model than what is possible in a human cohort.

It is important to consider that, in the context of preventive medicine in particular, the aim is to prevent abnormalities by subtle modulation over an *extended period*, so that maladaptation of the oxidative stress and inflammatory "control systems" of the body is slowed down or prevented. In the context of inflammation for example, a less subtle approach may lead to immune suppression of the individual, leaving him/her vulnerable to acute challenges. Of course, the exact nature of this subtle approach, which gives it long-term relevance and efficacy, also makes it near impossible to illustrate any effect in a healthy human population with huge statistical success, as an extended treatment period—with appropriate standardisation—

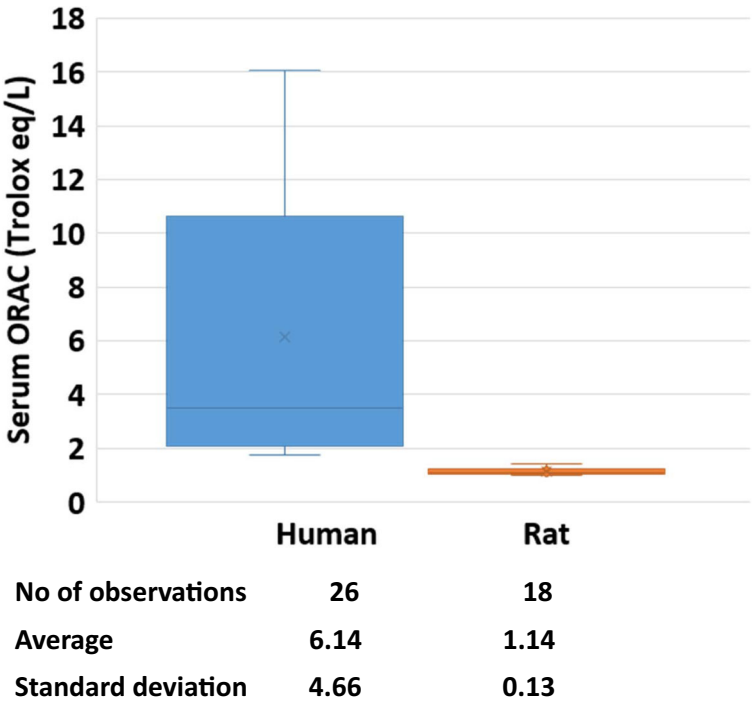

Fig. 2 A comparison of the expected variability in human vs rat models. Serum oxygen radical absorption capacity (ORAC) in absence of any intervention is used as representative example in the context of antioxidant research

would ideally be required. In rodents on the other hand, even a chronic protocol of relatively short duration represents a relatively bigger portion of total lifespan, given the fact that rodents age much faster than humans, who live approximately 30 times longer than rats [4], and may therefore more readily return statistically validated effects. The scientifically optimal solution would be that in addition to proof-of-concept and mechanistic studies using in vitro and animal models, longer term (over several years) epidemiological studies in humans be performed to definitively show long-term benefit of preventive medicines in the context of accelerated ageing and chronic disease development. Unfortunately, the long duration of these studies and the enormous costs involved may dissuade industry investment in this type of research.

Fortunately, an alternative exists. In our experience, a more imaginative examination of human data can provide a more comprehensive picture of potential effects in support of animal model data. For example, we were able to derive useful information on potential mechanisms of grape polyphenols from the first human treatment intervention study mentioned above [65]. As stated, basic analysis of variance did not indicate an effect of the intervention on Rho-associated protein kinase (ROCK)—a role player in effective directional movement of the cells—expression in neutrophils. However, using slightly more advanced confocal microscopy techniques, we were able to show that the co-localisation of ROCK with phosphatidylinositol-3-kinases (PI3Ks) was significantly lower after treatment, suggesting a modulation of the vitally important synchronisation of motility-control protein expression within the cell. This suggestion of an optimisation of the movement mechanics of phagocytic cells is in support of the in vitro studies showing improved neutrophil chemotactic movement after anthocyanidin pre-treatment [50]. Similarly, macrophage phenotype markers did not indicate a clear shift toward an anti-inflammatory phenotype in the human model. However, pre-treatment expression levels of the pro-inflammatory markers myeloperoxidase (MPO) and CD274 were negatively correlated with post-treatment levels, but in the anthocyanidin-treated group only (i.e. not after placebo treatment), again suggesting a modulatory role for grape seed extract, which may "normalise" the inflammatory profile to a more functionally optimal level. Again, this interpretation is in line with data from rodent and in vitro models. The conclusion from this is that more than just basic comparative statistical analysis is required, in order not to miss significant indications of efficacy.

Another data analysis and interpretation approach, which has already been adopted in the clinical health and exercise physiology literature [33, 46], is the interpretation of individual data rather than group average responses only. Figure 3 is a generic representation of actual data generated in our group, which illustrates the benefit of this approach. For both data sets illustrated, the variability of data at baseline, as well as the variability in effect of the treatment, was relatively high, so that for both the

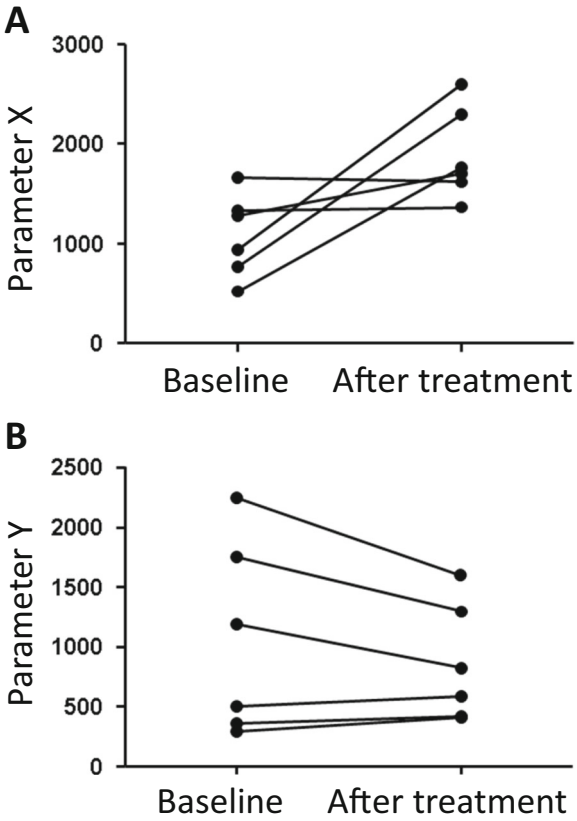

Fig. 3 Generic graphs (using actual data) illustrate the importance of considering individual data in addition to group averages, in order to detect treatment effects in more heterogeneous groups

statistical interpretation was that the treatment had had no effect. However, in frame A, it is clear that in individuals starting out with a low level of parameter X, the treatment effectively increased the level by at least 100% in all cases, while no effect was achieved in individuals with higher levels at baseline (i.e. those who were already at an optimal level?). Similarly, in frame B, the treatment only decreased the level of parameter Y if it started out relatively high, while already low levels were not decreased further. Interpretation of individual data may therefore not only lead to identification of results that would otherwise have been missed, but may also provide additional information on the profile of populations which stand to benefit most from the treatment. Given the high variability in human models, the general assumption that averages are indicative of group responses should be revisited.

Another potential obstacle in the preventive natural medicine niche is the prescribed sequence of clinical trials to be done. The studies described above, employed healthy and young subjects—a cohort requirement prescribed for phase 1 human clinical trials. However, since in these "normal" populations, there is still little requirement for improvement in terms of basal antioxidant and anti-inflammatory function, the expected effect size of a subtle modulator is too small to be detected above the normal variability of the parameters

assessed. The challenge here would thus be to convince ethics committees of the relevance of even very modest positive results such as the ones just highlighted—which were only evident after more comprehensive data analysis—in order to gain institutional and ethical approval for a next-phase clinical trial. Such follow-on studies, either in long-duration epidemiological follow-up studies, or in a more compromised population, where larger effect sizes can be expected due to the relatively larger maladaptive deviation from normal that would exist in such populations, would certainly yield more definitive proof of efficacy. However, currently, the dilemma is that research on many products is discontinued after these first-phase trials, on the basis of unrealistic expectations.

Impact of extraction technique and isolation of active ingredient(s)

A final methodological consideration specific to the assessment of natural products that deserves a special mention is the method of preparation of extracts. In another paper in this issue [8], the impact of the extraction process is clearly illustrated: while one extraction method produced an anti-inflammatory treatment, the other delivered an antioxidant with no evidence of any direct anti-inflammatory effect. Furthermore, the effect of any one substance is most probably modulated by synergy with other substances contained within the raw plant material [73]. This idea is further supported by more recent work on the antioxidant capacity of *Sutherlandia frutescens*, where the more basic extractions (hot and cold water), which are incidentally also more similar to the indigenous knowledge practitioners' preparation methods, illustrated far superior antioxidant capacity when compared to chemical solvent extractions [71]. A recent review on resveratrol observed that the idea of isolating single components from a plant in pursuit of a natural medicine is outdated, given the fact that the human diet consists of more than 25,000 substances [24]. Thus, in the context of plant products in particular, the conventional pharmacological technique of isolating and testing single actives for efficacy may not be a suitable methodological approach. Rather, selective propagation of plants to gradually modify the plant constituents and their relative distribution profile, or enrichment of existing plant material with purified actives, could be considered to achieve more therapeutic effect.

Concluding remarks

Given the aetiological importance of oxidative stress and inflammation in chronic diseases such as diabetes, they are clear targets in not only the therapeutic, but also especially in the preventive medicine niche. Given the many research groups dedicated to studying antioxidants and anti-inflammatories in the natural medicine niche, there can be little doubt that plant products—and in particular those from grapes—hold the key with which to unlock the answer to preventing maladaptive processes in the aetiological pathway to chronic diseases such as type II diabetes, cardiovascular disease, depression and even cancer.

Pharmacological and pharmaceutical paradigms and associated implementation guidelines designed for development of conventional and therapeutic medicines are currently directly applied to natural product research. This approach decreases the success of clinical studies in human cohorts, for a number of reasons that needs addressing. Firstly, the modulation achieved by a preventive medicine is relatively small when compared to a therapeutic medicine. Thus, the approach of a first-phase trial in healthy individuals dooms preventive medicines to failure. A suggestion here is that a result of "no detriment" should be sufficient to proceed to a trial in a more compromised cohort, so that positive effects may become evident. Secondly, plant actives seldom function in isolation—rather, synergy exists between many plant components. Thus, instead of insisting on the testing of isolated actives, or a comparison to single active standards or therapeutic medicine "controls", standardisation of plant extraction processes for any particular plant should be implemented and constituent concentrations monitored, to ensure maintained uniformity of the product offered to consumers. Thirdly, while in vitro and rodent models are most useful as proof of concept models or for mechanistic studies, researchers have to take the responsibility for using more advanced data analysis techniques in order to detect the more modest effects that should be expected in human models, which are naturally less controlled and thus more variable. In particular, in the context of inflammation or oxidative stress research, individual data may provide much more information without the necessity of doing expensive studies on huge cohorts.

In conclusion, the extensive indigenous, traditional knowledge that exists on the use of plant products to achieve medicinal effect cannot be ignored. However, it is the responsibility of researchers and policy makers alike to make paradigm shifts to accommodate this exciting avenue in medicine, in order to allow it to succeed.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

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