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editorial

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Can efficient delivery systems leverage benefits of antioxidants leading to potential medicines?

Despite the huge, largely untapped potential therapeutic benefit of functional foods that are rich sources of *antioxidants/vitamins,* there remains a general scepticism of the practice [1]. Evidence-based clinical practice will require proper, efficacious administration of an active component in functional food, rather than the continued reliance on traditional dietary means (which inevitably leads to poor bioavailability). The route of administration, dose and delivery play a very crucial role (this does not take into account the traditional medicine Ayurveda or Homeopathy) with respect to efficacy and this can be exemplified by the fact that venom may not be poisonous if it is ingested, rather than injected, as it contains high molecular weight proteins incapable of permeating the gut. Unfortunately, we still follow traditional dietary means, or use extracts filled in capsules to achieve therapeutic benefits where the active components of the herbs/functional foods/supplements may have been degraded before even reaching the systemic circulation. Unlike drugs, antioxidants purported therapeutic effect is predicated upon their ability to scavenge free radicals/prevent oxidative stress, however the choice of antioxidant was based on easy availability and not optimal antioxidant capacity, which is proposed as the major reason for failure of antioxidants in the clinic [2]. Epidemiological studies suggest that the low incidence of Alzheimer's disease in India is due to the consumption of the curry spice, curcumin and, in a similar vein, the low incidence of cardiovascular diseases in France has been linked to red wine consumption, but such studies have been far from conclusive.

According to Lipinski's rule of 5 [3], some of the most investigated molecules like epigallocatechin-gallate (EGCG), coenzyme Q10 (CoQ10) do not fulfil the criteria to suggest that they would be effective when administered orally; moreover they are not suitable candidates for administration by non-oral routes.

The majority of these compounds are available as extracts (excluding CoQ10) with high purity of active ingredient (often >95%). There are as many ~1750 clinical trials (http://www.clinicaltrials.gov) using antioxidants as supplements along with traditional drugs, while some are exploring the therapeutic benefits of antioxidants alone with majority of them offering moderate or no benefit, possibly due to poor oral bioavailability of antioxidants leading to mistrust of such chemical entities.

Interestingly, drugs that have been discovered as a result of their action against a specific, well-defined target have also been explored in a variety of other diseases with the rationale that the same or similar targets may have roles to play in other pathologies. For example, the anti-malarial drug, hydroxychloroquine, has been used to treat rheumatism in arthritis patients, but also has been shown to be useful in helping to maintain normoglycaemia in diabetes [5]. Similarly, Etanercept, which blocks the action of tumour necrosis factor-alpha (TNF) and is normally used to treat arthritis, also appears to reduce symptoms of dementia in Alzheimer's disease (AD) [5], whereas, in some cases, a clinical side effect may turn out to be clinically useful and in some cases, such

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as sildenafil sulphate (Viagra) may come to represent its most significant action. On the other hand we are not afraid of using molecules like warfarin for preventing thrombosis and embolism [6], which was initially used as a pesticide against rats and mice and is still widely utilised for this purpose. Even more interestingly, isolation of compounds from the venom of the deadly Brazilian pit viper led to the discovery of certain drugs to treat hypertension [7]. The key to the success here was due to the investigation of drug-likeness properties.

Advanced drug delivery systems not only allow product life cycle extension, but also can minimise attrition rates in drug discovery. Such delivery systems may hold huge potential for molecules like EGCG, CoQ10, curcumin and so on, that are almost completely ineffective when administered as conventional formulations. However, these delivery systems are applied only to existing drugs probably due to a lack of awareness or a biased approach. A more generous approach is required that can get the best out of the active substance using appropriate delivery vehicles. *For example, the potency of a new chemical entity could be improved by novel delivery strategies, not needing to take a more tedious approach to improve the potency of the active as such and end up making compounds that cannot be formulated.*

The author's laboratory conducted preclinical evaluation of co-encapsulated nanoparticles of CoQ10 and ellagic acid in a high fat diet rodent model [8]. The CoQ10 and ellagic acid combination could potentially reduce LDL levels comparable to that achieved by atorvastatin, a standard drug used for that purpose; however, the mechanism of the former is not known [8]. The depletion of endogenous levels of CoQ10 is believed to be responsible for many pathological conditions and hypertension is one such disease and supplementation of CoQ10 could be beneficial. The nanoparticulate CoQ10 is found to be efficacious in renal hypertension model, whereas the conventional CoQ10 offered no help in the model tested [9].

Despite significant developments in the delivery of cytotoxics, patients are looking towards oral supplements or other complementary and alternative medicines due to fear of the adverse side effects of chemotherapy (http://www.cancer.gov/cancertopics/cam). According to IMS Health, cancer agents comprise the single largest drug class with approximately a 7% share of global sales. At this juncture, it is important that we question our research hypothesis, is it mandatory that a cancer killing chemical should only be a cytotoxic, when several phytochemicals aided by better delivery systems have potential to outplay the cytotoxics [10]?

From the foregoing discussion [3,4] it is evident that one compound, one target do not really exist as a valid hypothesis anymore, rather one compound multiple targets could be a more attractive approach and the phytochemicals could be invaluable in several diseases that involve multiple pathogentic factors or for patients with co-existing diseases.

At the end of the day everything seems to boil down to glamour/glory, where academics are keen on making the problems as complex as possible that results in high impact publications followed by funding, where the industry is busy hunting for blockbusters that would keep their market share.

The progress in the area of herbs/antioxidants/supplements is hampered due to the following potential reasons: Antioxidant label; banking solely on free radical pathway; supplements; antioxidants are not new; no structure activity relationship; no preformulation; no proper formulation strategy; not treated as drugs; bypass regulatory agencies; IPR issues but the use of delivery system can solve this issue; acceptability issues; route of administration and dose can not be established. It is high time that we realise the potential of these natural molecules that can be potential medicines if delivered effectively.

On the other hand there is an increasing concern over regulation of non-conventional delivery systems such as nanotechnology based products further posing problems in antioxidant/nutrient delivery.

Medicine is all about risk versus benefit, therefore, a firm belief and an appropriate dose aided by suitable delivery systems can make better medicines by mitigating the risks.

Even if we don't get to a level of marketing medicines in an analogous way to cigarettes with captions such as: ''*can be injurious to health*'' and leaving it to the consumer to decide, ignoring the fact that passive smokers are most affected than active, we should at least make efforts to have regulation that facilitates better ideas, better medicines rather than posing problems/hurdles.

Conflict of interest

No conflict of interest declared.

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