Using Artificial Intelligence to Reduce Global Healthcare Costs through Discovery and Development of Nutritional Interventions

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Abstract: The human population is ageing and as age is a major risk factor for many of the top 10 causes of death worldwide, the ability to prevent age-related diseases and improve healthspan is of paramount importance. Nutritional interventions are cost-effective, easy to implement and scientifically proven approach to prevent disease and prolong healthspan. This research advocates evidence in the public domain proving nutrition can positively affect health. In relation to diabetes, plants belonging to the Fabaceae phylogenetic family have regularly demonstrated a positive influence on incidence and progression, in both humans and other animals. It would be advantageous for validated preventative nutritional strategies to be adopted by governments, globally. There are some barriers to the implementation of nutritional strategies as a mainstream form of treatment. In particular, the molecular complexity of food is great which adds a layer of difficulty in characterizing key actives within food and associating them to the relevant physiological target. In recent years, machine learning has been applied to different health areas, such as a functional ingredient derived from rice that significantly improves physical strength in an immune-impaired ageing population and a natural compound in pea that reduces cellular ageing. In summary, there is a major opportunity to use technology to identify novel, safe, natural compounds from food at a faster rate than ever before and to use this newfound understanding to prevent, treat and cure the most common serious diseases in the world today.

The human population is ageing at a rate that is unparalleled in the history of humanity as a result of declining fertility and increased life expectancies in different parts of the world [1]. In fact, the World Health Organisation predicts that between 2015 and 2050, the proportion of the world's population over the age of 60 will almost double from 12% to 22% [2]. Although over the past century modern medicine has improved our lifespan, in particular through improved infection control and public health initiatives, the economic and social issues arising from increased longevity are becoming critical. For example, simmering debates over pension schemes [3,4] and declining workforce sustainability [5,6] have extended to more fatal discussions concerning the future of funding the medical needs of older people [7–9].

With the proportion of older people among the global population now higher than at any point in human history and still expanding, maintaining health into old age (i.e. healthspan) has become a new and urgent frontier for modern medicine. Age is a major risk factor for most of the top 10 causes of death worldwide, such as ischaemic heart disease, Alzheimer's disease, cancer and the largest known human pandemic, diabetes [10,11]. Therefore, it is clear that while we are living longer, the ability to prevent the majority of age-related diseases and improve healthspan has not been successfully addressed. There are dramatic consequences of poor healthspan on public expenditure. In both the United States and Europe, 97% of public healthcare budgets are allocated to treatment, leaving only 3% to spend on prevention [12,13]. While such a model may have been sustainable in the past, these issues must be urgently solved as the pace of the entire globe ageing is increasing dramatically around the world. Over 150 years, France slowly adapted to a change from 10% to 20% in the

proportion of the population that was older than 60 years old. However, much larger countries such as Brazil, India and China have slightly more than 20 years to devise and implement the same adaptations [2].

Lifestyle medicine, the branch of medicine targeting traits such as diet, physical activity, treatment plan adherence and body weight control is rapidly emerging as a systematized scientifically-backed approach for chronic disease prevention and management. Numerous large-scale clinical studies have demonstrated that improving lifestyle metrics improves mortality from major causes of death such as heart disease [14–16] and cancer [17,18]. In particular, nutritional interventions are a cost-effective and realistic approach to prevent disease and to prolong our healthspan. Most people eat multiple times a day for their entire lives, providing ample opportunities to nourish our bodies with regenerative compounds that can positively affect chronic disease outcome. Therefore, it is imperative that preventative nutritional interventions backed by scientific and clinical proof are adopted by governments around the world. An increasing amount of research is showing that many of the top 10 diseases-causing deaths mentioned above can be prevented, or at least delayed, with nutritional therapy. As an example, the global incidence of type 2 diabetes continues to grow at an inexorable rate, currently affecting 425 million people, and is expected to afflict a further 204 million by 2045 [19]. While diabetes drug discovery has advanced significantly over the last two decades, in light of such widespread disease prevalence, there is an evident and urgent need for novel, safe, effective antidiabetic treatments [20]. Nutritional intervention as a form of therapy for type 2 diabetes is an active area of research that is being pursued rigorously by the scientific community. To demonstrate this point, we searched Google Scholar for the terms 'functional

food' and 'blood glucose regulation'. One hundred and ninety-one suitable research paper abstracts were examined, all of which positively demonstrated that the plant in question exhibited a pre-clinical or clinical blood glucose-lowering activity, predominantly tested in human (n=64), mouse (n=45) or rat (n=77). In the full data set of all species examined, it is clear that Fabaceae (the legume family) is the most commonly identified phylogenetic family exhibiting a positive association between a plant and blood glucose regulation, with 27 publications suggesting an effect (Figure 1). Specifically examining the sub-set of the data tested clinically in humans (n=64), there were a range of standard markers used to measure the change in blood glucose over

time, most commonly the oral glucose tolerance test, fasting blood glucose levels, hbA1c levels and fasting insulin levels, all of which showed positive associations between the ingredient and the trait. As with the full data set, the phylogenetic family most commonly associated with the trait in humans is Fabaceae, demonstrating an element of robustness to the association given the different species and tests conducted (Figure 1). Therefore, it is clear that even for this small example, some of the plants in this family are a potential target for the identification and characterisation of natural ingredients that can be developed to aid in lowering the T2D epidemic that the Western world is currently being consumed by.
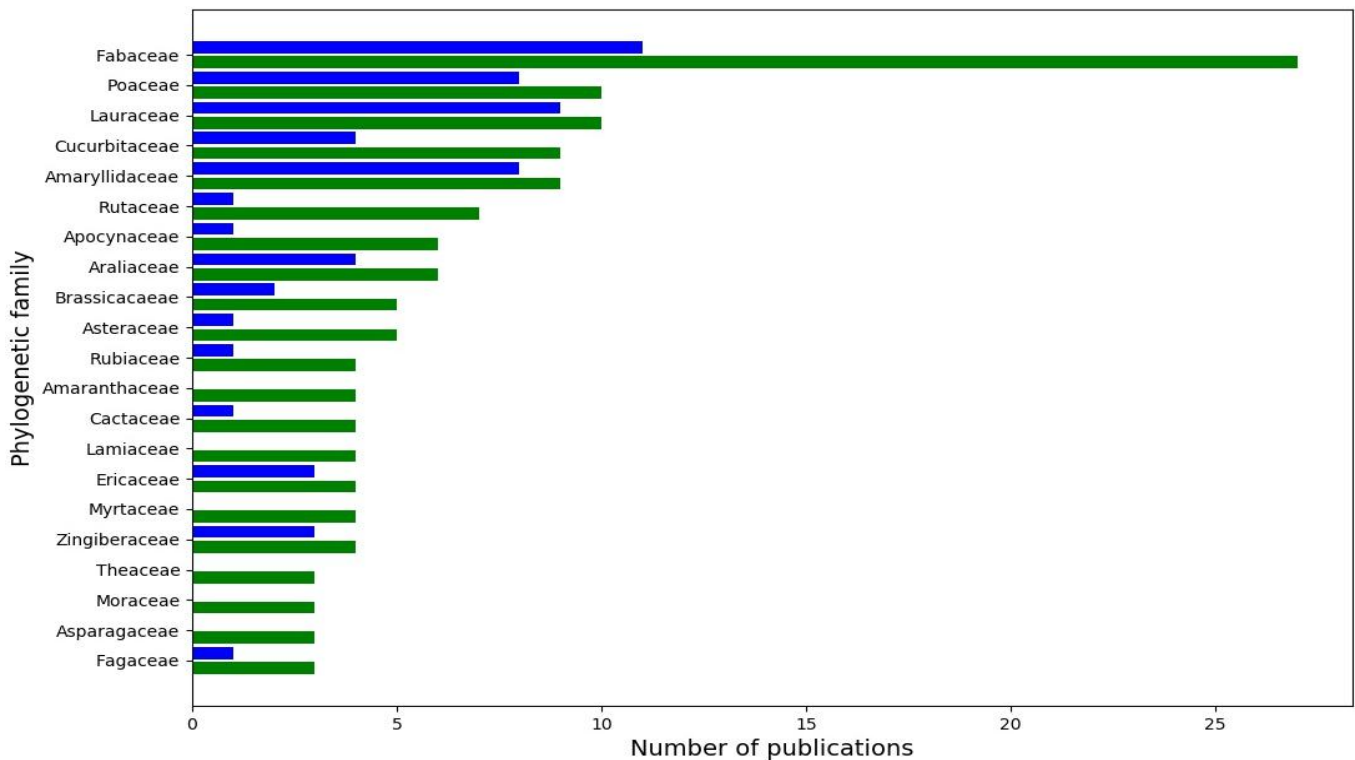

Figure 1. A review of phylogenetic families commonly positively associated with blood glucose regulation. The green bars indicate the number of publications, tested in human, rat or mouse, that were positively associated with blood glucose regulation. The blue bars are the sub-set of the data set that were specifically tested in humans. In both cases, the Fabaceae family, consisting of legumes, are most commonly positively associated with blood glucose regulation.

Given the obvious economic and public-adherence benefits to cost-effective, low-effort and scientifically-proven nutritional interventions to prevent and treat some of the world's biggest killers today, why are such approaches not being adopted as a mainstream form of therapy? The primary reason is that there is no global consensus on functional food strategies as interventions. To understand this, one needs to look closer at the pharmaceutical industry and how they succeeded in becoming a mainstream strategy and implement those learnings to support a mainstream functional food strategy. Indeed, the pharmaceutical industry maintains high standards and regulatory frameworks *in situ* to ensure efficacy and safety of well-defined key medical compounds. The success of the pharmaceutical area comes as a result of many factors including; the existence of robust regulatory frameworks, excellent understanding of the therapeutic itself, consistent and quality-controlled production lines, supportive government reimbursement and patent protection schemes. These measures, combined with continuous validation and quality protocols, contribute to the reproducibility of drug

intervention strategies. Similar standards must be maintained for the widespread adoption by global public healthcare of functional ingredients.

However, unlike pharmaceuticals, where the active compound is refined and pure, the identification, characterisation and development of a natural ingredient is much more complex. Instead of one pure molecule as is common for pharma to develop, a functional food, such as a plant, would contain trillions of molecules present at different concentrations. It is difficult to decipher in those trillions, the activity carried by each individual molecules, if any. This molecular complexity of a food such as these plants is unparalleled, and similar to space exploration it creates a massive mathematical problem waiting to be solved. Traditional methods to understanding the bioactivity of molecules in plants or other sources such as milk or marine sources has relied on iterative random lab testing of different fractions of the source material, followed by purification and testing. This time-consuming and expensive approach has led to relatively few impactful functional

ingredients given the effort required. However, plants are full of medicinal properties that so far have not been tapped into. This mathematical complexity of these different natural sources, such as plants, means that the extraction and identification of all their life-saving compounds will never be solved through random approaches but needs methodical application of the latest technologies, namely artificial intelligence (AI), that can sufficiently process such vast amounts of molecular data.

Machine learning (ML) is a technology belonging to the artificial intelligence family that fits statistical models to data to learn trends in the data; these models can then be applied to other data sets to understand them further. To date, the most common application of machine learning to healthcare has been in diagnostic and precision medicine. For example, ML algorithms are already outperforming radiologists at identifying malignant tumours [21], and are also predicting what treatment protocols are likely to succeed on a patient based on various attributes [22]. Another recent exciting application of machine learning to healthcare has been in the identification of molecules with specific therapeutic effects. Peptides are short chains of amino acids that are found in all living organisms and play a key role in various biological functions, such as immunity, inflammation and blood glucose regulation. Recently, there has been a dramatic increase in the public availability of peptide sequence databases that are used to power some machine learning approaches. For example, databases of peptide sequences and their manually curated experimental effects on various diseases now exist for many major diseases, including peptides with the ability to kill bacteria [23–28] and viruses such as HIV [29], hypertension [30] and cancer [31]. AI approaches, such as ML, have leveraged this explosion in publicly available scientific data with state-of-the-art algorithms to successfully identify which biological peptides in plants, out of the million peptides that exist in any one source, are likely to exert a positive effect on various life-threatening diseases. For example, bioactive peptides sourced from the rice plant were recently fully characterised and shown to have immuno-modulatory effects in human [32]. Another AI discovery characterised a functional ingredient, again derived from rice, that significantly improved physical strength and mobility in a double-blind placebo with an immuno-impaired ageing population [33]. Additionally, a similar approach identified a peptide within the pea plant that reduced cellular ageing in a double-blind placebo clinical trial [34], while other research proved that a peptide hydrolysate from fava bean has the ability to prolong muscle health [35]. Such examples demonstrate that the complexity of understanding the clinical benefits of plants can begin to be solved by the latest ML algorithms and that plant-derived functional ingredients can now be developed in a scientific manner at a minute fraction of the costs traditionally associated with pharmaceutical development.

We are currently witnessing a revolution in the landscape of disease and medicine as we know it, as we unearth novel, scientifically-proven compounds from natural ingredients faster and cheaper than ever before. Even more encouragingly, the process of developing functional ingredients, both with and without ML techniques, is

becoming more defined and rigorously controlled, making these ingredients more comparable to pharmaceutical compounds. Across the globe, the scientific community is actively pursuing the best way to regulate [36–39] and characterise [40] these ingredients. Research is commonly concluding that investment in functional foods is a significant market with large development for potential worldwide [41–43], which paves the way for government reimbursement and patent protection schemes, akin to those available to the pharmaceutical industry.

Similar to the difficulties being faced with the application of nutritional interventions to prevent life-threatening diseases, the greatest challenges that AI in healthcare domains has faced so far is not whether the technologies will be capable enough to be useful, but rather working out the best practises for identifying which components are most useful for different situations (in this case, illnesses), and adoption into daily clinical practice. It is becoming increasingly clear that relying solely on the classic pharmaceuticals to cure, treat or prevent the biggest killers facing humans today is a failing model. For example, most antibiotic chemical scaffolds in present clinical use were discovered > 50 years ago and some opinions suggest that the days of finding highly potent, non-toxic, broad-spectrum and inexpensive drugs are over [44]. By contrast, the identification of anti-microbial therapeutic peptides is just beginning, as recent research implemented ML methods to identify a peptide that is not only anti-microbial, but potent against *Acinetobacter baumannii*, a pan-drug resistant microbe [45]. Peptide therapeutic discovery, some of which also incorporate ML-based research, will also allow us to respond quickly to new emerging epidemics where traditional pharmaceuticals have yet to provide an adequate treatment, as has been demonstrated through the intense and promising investigation of peptides as potential SARS-CoV-2 (COVID-19) therapeutics [46–48]. Developing traditional pharmaceutical drugs is also costly, for example, one recent study found the cost of developing a cancer drug to be in the region of $648 million [49]. Ultimately, one of the biggest challenges currently facing the human race is how to treat the explosion of age-related disease cases that are being observed globally, while maintaining healthspan as long as possible, in an economically viable manner. The answer is surprisingly simple. Nature has already given us the solution through the abundance of disease-defeating molecules in plants, and science is finally catching up with tools to mine these molecules quickly and safely. Applying AI nutritional intervention disease therapies to address the world's deadliest diseases are not only overdue, but imperative to increasing the healthspan and maintaining global economic equilibrium over the decades to come.

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