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Review Article

Peptide Therapeutics in the Post-AlphaFold Era: Current Advances, Pharmacokinetic Strategies, and Future Opportunities

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ABSTRACT:

Food is no longer seen simply as a source of calories and vital nutrients. Instead, it is increasingly understood as a daily biological exposure that can affect inflammation, oxidative stress, insulin sensitivity, vascular function, the gut microbiota, and the risk of long-term chronic diseases. The idea of "food as medicine" involves using evidence-based dietary approaches in a deliberate way to help prevent disease, improve clinical outcomes, and complement standard medical treatment. This does not mean that food should replace medication. Rather, nutrition should be built into clinical care in a way that is safe, personalized, and carefully monitored. This review outlines the biological foundation of food as medicine, the clinical evidence in cardiovascular disease, type 2 diabetes, and cognitive health, and the role of pharmacists in handling food–drug interactions, supplement use, and medication safety throughout dietary changes.

Keywords: *Food as medicine; chronic disease; nutrition therapy; inflammation; gut microbiome; cardiovascular disease; type 2 diabetes; food–drug interactions.*

1. INTRODUCTION

Chronic diseases almost never come from a single source. They are usually acquired over a long period by the interplay between genes, behavior, the environment, drug therapy, social environment, and metabolic risk. Food intake is one of the major modifiable risk factors in chronic diseases. While unhealthy dietary patterns contribute to the pathogenesis of obesity, hypertension, dyslipidaemia, insulin resistance, cardiovascular disease, and type 2 diabetes, healthy food patterns will help decreasing risk and achieving clinical control, and this has led to the phrase "food as medicine" is frequently heard in medical settings(Afshin et al., 2019; Downer et al., 2020; Katz & Meller, 2014).

This should be used with caution; food as medicine does not imply that food can cure all conditions or substitute all medicines. Food as medicine actually implies that food can be used in a way to treat a disease if it is evidence-based and clinically applicable and has to be monitored. In certain condition, the food intervention can result in reduced medicine intake or remission as in early stages of type 2 diabetes. For some conditions the food cannot substitute medicine but will work with it, for instance it can be used for support of a treatment in patients with advanced cardiovascular disease and patients under anticoagulation therapy(Downer et al., 2020; Holbrook et al., 2012; M. E. Lean et al., 2018).

Food as medicine can best be illustrated through dietary patterns, as opposed to specific foods called "superfoods". These are diets rich in vegetables, fruits, legumes, whole grains, nuts and seeds, and also include fish and unsaturated oils. They provide dietary fiber, vitamins, minerals, polyphenols and other biologically active compounds, all acting in a concert. They have been shown to attenuate inflammation, oxidative stress, endothelial function, control over blood glucose and modification of gut

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microbiota. They are responsible for why diet can affect multiple diseases simultaneously(Cryan et al., 2019; Furman et al., 2019; Katz & Meller, 2014) [1,4,5].

Nutrition is a topic of interest to pharmacists because the relationship between food and medicines is inherent in the daily lives of patients. Patients are likely to be consuming a low-carbohydrate diet while also taking insulin, a low-fiber diet while also taking warfarin, to be consuming a leafy-green-rich diet while also taking warfarin, consuming grapefruit juice while also taking a drug that is metabolized by CYP3A4, and/or to start an herbal therapy such as turmeric, fish oil, or herbs, without providing information to pharmacists. Nutrition therapy is inseparable from the safety of drug therapy and pharmacists are in a unique position to provide safe food-based care through interactions, promoting adherence, and communicating with prescribers when drug adjustments are warranted(Bailey et al., 2013; Greer et al., 2016; Holbrook et al., 2012) [14,15,22].

2. BIOLOGICAL BASIS OF FOOD AS MEDICINE

The biology behind using food as medicine starts with chronic low-grade inflammation. Acute inflammation protects the body when injured or invaded, however chronic inflammation may develop and remain subclinically, promoting atherosclerosis, insulin resistance, complications of obesity, chronic kidney disease and neurodegeneration. Foods high in refined carbohydrate, added sugars, processed and ultra-processed meats can trigger inflammation signaling. However, a plant-rich dietary pattern and unsaturated fatty acids can help lower inflammation burden(Furman et al., 2019).

Oxidative stress is also one important mechanism. Overproduction of Reactive oxygen and nitrogen species can cause damage to lipids, proteins, DNA, and vascular cells. A number of foods have components that have ability to stimulate the cell defensive system. Polyphenols are common components of many foods such as berries, tea, coffee, cocoa, herbs, spices, legums and olive oil, which may affect antioxidant response signaling pathway, inflammatory pathway and endothelial cell function and gut microbiota metabolism. Nevertheless, polyphenol cannot be treated as a 'miracle antioxidant' as there depends on Food matrix and metabolism as well as overall dietary habits over long time(Katz & Meller, 2014).

The gut microbiome is also the one of the most convincing mechanisms proposed to explain diet's effects on health in non-caloric terms. Microbial fermentation of dietary fiber derived from foods such as vegetables, fruits, pulses and whole grains into the short-chain fatty acids acetate, propionate and butyrate helps to promote barrier integrity, control the immune response and maintain metabolic signaling within the gut. A Western diet low in fiber has been shown to decrease gut microbial diversity and may contribute to dysbiosis whereas fiber rich dietary patterns may promote a more healthy microbial environment(Cryan et al., 2019; Koh et al., 2016).

Also it has been suggested that the microbiome could be involved in relating diet to brain function. The gut-brain axis works through a variety of pathways including immune signalling, microbial metabolites, the vagal route, tryptophan metabolism and neuroendocrine signalling. While this is an area which is only in its infancy, it shows that it may be plausible for diet to affect mood, cognitive function, neuroinflammation and the risk of neurodegenerative disease. These pathways are intriguing but care must be taken when describing them-diet can be said to promote brain health rather than 'cure dementia'(Barnes et al., 2023; Cryan et al., 2019; Morris et al., 2015).

In addition to the effects on other hormones and enzymes in glucose metabolism, foods also influence glucose metabolism and insulin sensitivity. Diets that consist of readily absorbed carbohydrates (e.g., refined carbohydrate foods) and added sugar may promote higher postprandial glucose peaks and enhance the progression of insulin resistance in susceptible individuals. Conversely, dietary habits characterized by adequate dietary fiber, whole carbohydrates, unsaturated fat and adequate protein, may promote satiety and lead to improved glycemic control and lipid profile. Reduction of weight, particularly the amount of liver and pancreatic fat, is considered crucial in

management of type 2 diabetes(Berry et al., 2020; M. E. Lean et al., 2018).

At the same time, the same diet does not elicit the same response in all individuals. Genetics, gut microflora, medicines, sleep, exercise, stage of disease and initial metabolic state can modify postprandial glucose and lipid response, so a precision approach could guide diet based on these data. However, for a personalized approach to care, we do not necessarily need complicated tests, but could initiate personalization on the basis of common clinical parameters such as diagnosis, medicines, HbA1c, kidney function, lipids, blood pressure, culture, social background, family history and access to food(Berry et al., 2020; Downer et al., 2020).

3. CLINICAL EVIDENCE IN CHRONIC DISEASE

This is an extremely strong clinical area for food as medicine. Cardiovascular disease. There are more studies examining the Mediterranean diet than any other food pattern with respect to prevention. Cardiovascular risk and those assigned to a Mediterranean diet with additional virgin olive oil or nuts/mixed nuts had less major cardiovascular events than those assigned a low-fat diet in Prevención con Dieta Mediterránea trial. Most significant as this was a randomized clinical trial. Not just an observational study(Estruch et al., 2018).

The protective effect of the Mediterranean diet might be explained by the whole dietary pattern and not by a specific nutrient: monounsaturated fatty acids and polyphenols from the olive oil; unsaturated fatty acids, fiber and minerals from the nuts; whole cereals and legumes for a better glycemic control; omega-3 from fish; and potassium and bio-active components from fruits and vegetables. These might enhance the endothelial function, lipid profile, blood pressure, oxidative stress and inflammation(Estruch et al., 2018; Furman et al., 2019; Katz & Meller, 2014).

Type 2 diabetes is an area of major importance where modification of diet can impact prognosis. The diabetes remission clinical trial reported that intensive dietary weight management could cause remission of newly diagnosed type 2 diabetes with participants undergoing a period of total energy restricted dietary replacement, food reintroduction and maintenance support. At 12 months, the remission rates for the intervention group was 46% versus 4% for those having usual care suggesting it is disease-modifying in specific patient groups using an food based intervention (M. E. Lean et al., 2018).

The 2 year results of diabetes remission clinical trial indicate remission is achievable but can be hard to sustain long term. This is important clinically since dietary treatment is not a finite prescription; follow up, relapse prevention, behavioral support and review of medications are necessary. The likelihood of achieving remission seems greatest in patients with shorter duration of diabetes, who are overweight or obese and who have adequate beta-cell reserve. Remission of diabetes in certain individuals needs to be offered as a possibility rather than a guarantee(M. E. J. Lean et al., 2019).

Also, the use of a low-carbohydrate diet in type 2 diabetes has been evaluated. A systematic review and meta-analysis of low-carbohydrate and very low carbohydrate diets has suggested a potentially beneficial role of these dietary strategies in glycemic control and remission in six month time frames; at 12 months the benefit seems less clear. These data indicate that a carbohydrate restriction may be beneficial for some patients, but the usefulness is determined by factors such as compliance, food quality, safety and the clinical context of each patient. A low-carbohydrate diet made of vegetables, nuts, olive oil, fish and other minimally processed foods does not equate with a low-carbohydrate diet consisting of meat, processed meats and saturated fats(Goldenberg et al., 2021).

Dietary habits may also affect cognition, though this relationship is even less established than that between diet and cardiometabolic disease. Adherence to a dietary pattern that emphasizes leafy greens, berries, nuts, legumes, whole grains, fish, poultry, olive oil, and moderate amounts of dairy and limited intake of red meat, butter, cheese, sweets and fried foods (combining aspects of the Mediterranean and DASH diet plans)-referred to as the MIND diet-has been shown to correlate inversely with incidence of Alzheimer disease in a prospective cohort(Morris et al., 2015).

Evidence based on randomized trials of cognitive endpoints is equivocal. One randomized controlled trial of the MIND diet showed no clear cognitive benefit over the control diet over the course of the trial although the groups improved in certain areas. This does not rule out benefit of the the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet. This simply means that perhaps the cognitive decline must occur even earlier, for a longer time and require the combined effect of several risk factors before benefits from diet can be demonstrated. Nutrition in support of the aging brain should be thought of as risk prevention and not a treatment for dementia(Barnes et al., 2023).

On balance, the clinical evidence suggests a balanced message. The evidence for the role of diet in the prevention of cardiovascular disease and management of type 2 diabetes is strongest. The evidence for the role of diet in cognitive prevention is tentative. Food can be seen as both disease preventative and disease controlling, and occasionally as reducing drug burden; however, it is appropriate to incorporate diet with a medical regime rather than as a panacea(Downer et al., 2020; Estruch et al., 2018; M. E. Lean et al., 2018).

4. FOOD–DRUG INTERACTIONS AND THE ROLE OF PHARMACISTS

Food-based care is clinically relevant when used in conjunction with pharmacotherapy. Chronic disease requires polypharmacy and a modification of diet could potentially affect a drug's effect, safety and require specific monitoring, the central reason why a pharmacist plays a key role in the safe use of food as a medicine. Rather than substituting dietitians, the pharmacist's responsibility is in recognizing medication-related risks and food-drug interactions, in addition to reviewing supplement use and promoting dialogue with the prescribers(Greer et al., 2016; Holbrook et al., 2012).

An old reliable example of this interaction is warfarin and vitamin K. The mechanism of warfarin involves the inhibition of vitamin K-dependent coagulation factor synthesis and hence any drastic alterations in vitamin K intake will alter INR control. The message is not that green leafy vegetables should be avoided. Doing so may result in a reduced dietary quality. A much better, more practical message is one of stability. Vitamin K intake should be constant and any large dietary changes reported to the clinical team(Holbrook et al., 2012).

Grapefruit juice is another classic example of a drug interaction. Grapefruit juice contains furanocoumarins, which inhibits intestinal CYP3A4, and leads to a higher bioavailability of some orally ingested drugs. This can be clinically significant for specific calcium-channel blockers, immunosuppressants, antiarrhythmics, and some statins. This interaction is, however, drug-specific. Generic warnings should not be given, and advice should be based on specific medication lists(Bailey et al., 2013).

Supplements also require careful review. Fish oil, turmeric, garlic, green tea extract, protein powders, and weight loss supplements are a few of the many things people take that they don't consider drugs. For example, the bioavailability of curcumin is low, but when combined with piperine the absorption is increased. While this might sound helpful this may also present safety concerns in a patient taking anti-coagulants or anti-platelets and also chemotherapy or other chronic medications. It is important that pharmacists ask about these supplements in a non-threatening way so that patients feel safe admitting taking them(Hewlings & Kalman, 2017; Shoba et al., 1998).

It will also affect drug requirement. In patients with type 2 diabetes, substantial weight reduction or low carbohydrate intake can decrease glucose rapidly, this puts patients on insulin or sulfonylureas at risk of hypo-glycaemia. A change in diet can result in weight reduction, decreased sodium intake and better quality diet, which subsequently leads to reduction in blood pressure, that needs re-evaluation of anti-hypertensive regimen. While beneficial, these effects should be monitored(Goldenberg et al., 2021; M. E. Lean et al., 2018).

Practical problems like fasting are also a real issue. Some of our patients are religious and would fast for religious purposes and others do intermittent fasting for metabolic health/weight loss. It would seem to be beneficial for some of our patients in reducing calorie intake and improve metabolic flexibility, but

it would not be suitable for everyone. Patients taking insulin, sulphonylureas, diuretics and other drugs that require medication to be taken with food should be counselled individually on the issues, with respect to timing, recognise warning symptoms and when medical help should be sort(De Cabo & Mattson, 2019).

A very basic and pragmatic approach to a pharmacist- led system could include the following: When reviewing medication, ask the patient if they have altered diet, been fasting, lost weight, consumed grapefruit, increased consumption of leafy green vegetables or taken supplements. This may provide much clinically relevant information that will not be included in prescription data. In instances where risk is detected, offer counselling, monitoring or contact with the prescriber (Downer et al., 2020; Greer et al., 2016; Holbrook et al., 2012).

The role of the pharmacist in education also extends to clarification. Patients might have beliefs that naturally derived products are always safe and that following a diet plan, allows them to discontinue medication. A sensible balance is required - while the diet will enable positive health effects, and sometimes allow for reducing medication, changes to medication require a clinical basis(Downer et al., 2020; Medhat et al., 2020). In this context, the pharmacist becomes a link.

5. CHALLENGES, LIMITATIONS, AND FUTURE DIRECTIONS

The role of food as medicine holds promise, however, research on the relationship between diet and health is problematic. Individuals eat combinations of nutrients rather than individual nutrients. Subjects that eat healthily may also be more active, may smoke less, sleep more and/or have better access to healthcare. Thus, establishing a cause-and-effect relationship from an observational study is not possible. It does not make nutrition research pointless; however conclusions must be tempered(Ioannidis, 2018).

Measurement of diet also represents a barrier to this research. A number of studies use a food-frequency questionnaire or a dietary recall (both self-reported measures). Whilst these methods are practicable, they are far from accurate; patients may fail to recall items that they consumed, recall only a portion of the amount consumed and record a more healthy diet than actually experienced. Randomised trials can minimize certain aspects of bias, but are challenging as people are aware of their diet and maintenance over a period of time is problematic(Ioannidis, 2018; Trepanowski & Ioannidis, 2018).

Additionally, the plethora of popular diets has contributed to this uncertainty. For instance, low-carbohydrate diets, ketogenic diets, intermittent fasting, detox regimens, and supplement-dependent programs are frequently promoted online, with overstated purported benefits. While certain approaches might be beneficial for select patients, they could be hazardous if used without consideration of medication use, renal status, pregnancy, eating disorders, frailty, or chronic disease severity. The real issue in the clinic is not if the diet is trendy but whether it is safe, effective, affordable, acceptable and sustainable for the patient(De Cabo & Mattson, 2019; Goldenberg et al., 2021).

Additional sources of confusion include issues of conflict of interest.Nutrition studies can be funded by the food and beverage industry, supplement manufacturers, or by companies that produce weight loss products. The mere presence of funding by such entities does not prove a study is invalid, but it could affect the types of research questions asked and the conclusions drawn and communicated to the public. This is one reason that the research should be considered in light of who is funding it, be duplicated independently if possible, and be carefully read (especially methods) if the findings are being used to influence public health or clinical practice(Bes-Rastrollo et al., 2013).

Education of health professionals also requires work. Nutrition knowledge and education for many pharmacists, physicians, and other healthcare providers is inadequate. Pharmacists would benefit from future education regarding therapeutic nutrition, supplement risk management, food-drug interactions, culturally competent counseling, and referral resources. This is not a re-training of pharmacists as dietitians, rather the ability to understand drug-nutrition-disease related risks and

counsel effectively(Greer et al., 2016; Medhat et al., 2020).

Food- as- medicine is not utopian; it needs to move beyond blaming patients for their illnesses and societal issues and beyond claims of "cures." It needs to offer a framework for providing clinical and practical dietary support and medication safety reviews along with access to good food wherever possible. The most valid form of intervention appears to be interprofessional where a doctor or nurse practitioner diagnoses and treats illness while a dietitian provides thorough dietary assessment and meal plans. A pharmacist is also critical to the care team for reviewing medications to minimize the risk of interactions. Patients should be active participants in their own health(Downer et al., 2020; Greer et al., 2016).

6. CONCLUSION

"Food as medicine" needs to be thought of within the framework of evidence-based health care rather than as an adjunct or alternative. Foods can modulate inflammatory responses, oxidative stress, gut microbial metabolism, insulin sensitivity and vascular function as well as long term disease risk. We have compelling clinical evidence supporting Mediterranean dietary approaches to cardiovascular prevention and structured weight loss approaches in certain type 2 diabetic patients. The evidence for cognition support is encouraging and should be read with care(Cryan et al., 2019; Estruch et al., 2018; Furman et al., 2019; M. E. Lean et al., 2018).

Food can cure and assist treatment, improve clinical parameters, potentially reduce medication requirements, and the healthiest message to convey is a middle ground where food is recognized as such and not as a universal replacement to pharmacotherapy. Chronic disease patient requires both dietary intervention and pharmacotherapy and it should be the role of health professionals to merge them and not divide (Downer et al., 2020; Holbrook et al., 2012).

Pharmacists are at the forefront of this integration. Pharmacists can prevent or address drug–food interactions, screen and review supplements, assess for risk when major changes are being made to one's diet, enhance adherence and collaborate with the rest of the healthcare team. When these factors are considered by pharmacists, food as medicine will move from trendy term to a safer, functional intervention that aids in managing chronic diseases(Greer et al., 2016; Medhat et al., 2020).

In summary, food is no panacea, yet it is too crucial a factor to be allowed to continue excluded from the clinic. When dietary interventions are evidenced based, culturally feasible, economically sustainable and integrated with pharmacotherapy they can be transformed from a largely unused luxury into one of the most effective tools available in managing modern chronic disease.

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