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Review

Nutraceuticals in Personalized and Precision Medicine – a preliminary scoping review indicates efficacy for disease treatment, general wellbeing, and defense against Covid-19

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ABSTRACT: Nutraceuticals have taken the spotlight during the past two decades as evidenced by the exponential publications on them. Long a part of routine in Traditional Medicine Systems, the rise of their mainstream use globally raises both safety concerns and need for better understanding of efficacious dosing. We attempt to answer these questions in this preliminary scoping review by an analysis of current literature on nutraceutical use as a personalized or prescription medicine. Using Covidence, Rayyan, and manual searches of PubMed, 598 unique publications were selected. 32 are systematic reviews, of which we overview the scope. We also overview 30 papers that address adverse drug reactions. To obtain an unbiased landscape of the 598 papers, we analyzed keywords using multiple methods. Expectedly, the most frequent keywords were probiotics and vitamins. Unexpectedly and remarkably, among the highest keyword yield was 'COVID'. Further exploring this aspect, we review 15 pertinent papers, that not only provide robust evidence for nutraceutical benefits as part of SARS-CoV-2 treatment, but also amplify the notion that nutraceuticals are protective. Overall, the strident note is that further robust targeted research is needed in order to reap the full benefits of nutraceuticals in a safe and efficacious manner.

KEYWORDS: Nutraceuticals; Personalized Medicine; Precision Medicine; Probiotics; Vitamins; Covid; Dietary Supplements; Adverse Drug Effects

INTRODUCTION

The new millennium of which we are still very much in its infancy, has nevertheless produced revolutionary changes in medical and scientific interests. Among the causes for this is an emergence of renewed interest in traditional healing systems, especially in the context of holistic living. Perhaps as a reaction to the western medical system's (which we will henceforth refer to as world mainstream medicine (WMM)) relentless emphasis on breaking down the whole to its individual parts, attention in the past few decades has shifted to traditional medical systems (TMS) which focus on the person as a whole as an alternative methodology of approach to disease prophylaxis and

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therapeutics. The interested reader is referred to the WHO TMS report that summarizes this attention [1]. Among the main TMS axes discussed by the WHO, are the roles of diet and nutrition, which is the focus of this review. In fact, the burgeoning interest in the importance of nutrition as a form of medicine has gained such a quick and exponential rise in the past two decades that it has formed its own field, that of what is termed 'nutraceuticals' or the use of nutrition as a pharmaceutical agent. A simple PubMed query for the term sans any filters yields 108,073 results. 118,774 results using the American English spelling of 'nutraceuticals' (which we will adopt in this paper) as of October 28th 2022, with publications exponentially rising in number since the new millennium dawned. In this mini scoping review, we will examine the existing literature with a specific focus on the impact of nutraceuticals as agents in precision and personalized medicine.

First let us iron out the difference between precision and personalized medicine, detailing the nuances of applying nutraceuticals in both contexts. We have elaborated elsewhere on the subtle distinction between the two[2], here we may briefly state that while precision medicine focusses on identifying and treating the specific root cause of the disease (e.g., identifying a specific genetic lesion that induces a particular profile of said disease), personalized medicine does the same however focusses on the individual patient as the particular or 'precise' profile of said disease. In other words, while the patient's lifestyle, genomic background, environment etc., contribute to a particular precision disease profile in the latter, that is not necessarily the same focus in the former. Thus, we see that personalized medicine rather than precision medicine, is the discipline most aligned with the philosophy of TMS which always consider the individual patient as the nexus[3]. Conversely, it may be argued that the precision medicine approach in that it aims to pinpoint cause of disease in higher resolution than previously possible is actually a rarified instance of the WMM's philosophy of compartmentalization. And hence these two terms, though often used interchangeably, are ironically both philosophically contrasting yet practically coinciding. Indeed, the field of nutraceuticals, that originated from the TMS philosophy of the individual as a 'whole', is now generally understood as an entity morphed with the WMM precision-pharmaceuticals approach of delivering nutrition as a pharmacological agent with pinpoint accuracy. Regardless, current literature often clumps efforts in persolized and precision medicine together. Hence it is difficult to tease apart current evidence for nutraceutical impact among the two. We therefore address both together in this article.

METHODS

Survey of existing literature and filtering unique publications

PubMed was searched for nutraceuticals with either precision medicine or personalized medicine in October 2022. PubMed's search algorithms automatically include the MeSH term 'dietary supplements' and its derivations. Complete search MeSH terms are in supplementary note. Records were downloaded, and duplicates removed using Rayyan.ai[4], Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. available at www.covidence.org), and manual data analyses using MS Excel, and BASH scripting.

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Screening and filtering unique articles

Unique publications were screened by using Rayyan.ai, Covidence, and by manual data analyses. MS Excel data filtration tools, and Windows Powershell BASH scripting was used to conduct counts of keywords.

RESULTS AND DISCUSSION

Searching PubMed for 'neutraceuticals and personalized medicine' yielded 502 publications, while the American spelling 'nutraceuticals' yielded 596. Searching for 'neutraceuticals and precision medicine' yielded 292 publications, and 352 for the version with American spelling. Merging the respective searches and removing duplicates, resulted in 598 unique records for nutraceuticals and personalized medicine (*file A*) and 353 unique records for nutraceuticals and precision medicine (*file B*). Merging both *A* and *B* files and removing duplicates resulted in 598 unique records, which were not entirely surprisingly, the exact records found in *file A*. Thus, *file B* was always a subset of *file A*, corroborating our prior assertion that current literature rarely addresses the distinctions between personalized and precision medicine. We then used this final merged file, for which we will retain the name *file A*, to conduct our scoping review. First, we filtered out all SRs and manually assessed them. We have assumed that relevant Randomized Controlled Trials (RCTs) will be addressed by the SRs. Second we screened for reports of drug interactions, reports involving genomics or derivatives thereof (such as pharmacogenomics) and manually assessed them. Below are details of findings from both these scoping analyses.

Systematic Reviews (SRs)

Of the 598 articles, Rayyan yielded 24, Excel yielded 28 and Covidence yielded 32 publications as SRs. Merging these resulted in 32 unique publications (Table 1). The Covidence yield included those from the other two filtrations. The final 32 publications include four[5–8] (selected by Covidence) that are not strictly SRs, however we have included them in our analyses due to the relevance of their scope. Below is a scoping overview of their content.

Table 1: 32 Systematic Reviews on Nutraceuticals in Personalized and Precision Medicine.

	Title	DOI	Comment
1	Cholinesterase inhibitors and add-on nutritional supplements in Alzheimer's disease: a systematic review of randomized controlled trials	10.1016/j.arr.2014.06.002	Alzheimer's
2	Nonoperative Treatments for Knee Osteoarthritis: An Evaluation of Treatment Characteristics and the Intra-Articular Placebo Effect: A Systematic Review	10.2106/JBJS.RVW.17.00167	Arthritis
3	A comprehensive systematic review and meta-analysis of pharmacological and dietary supplement interventions in paediatric autism: moderators of treatment response and recommendations for future research	10.1017/S0033291716003457	Autism
4	Dietary Supplements in People with Metastatic Cancer Who Are Experiencing Malnutrition, Cachexia, Sarcopenia, and Frailty: A Scoping Review.	10.3390/nu14132642	Cancer
5	Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review	10.1016/j.clnu.2013.06.012	Cancer

6	Exploring the effect of microecological agents on postoperative immune function in patients undergoing liver cancer surgery: a systematic review and meta-analysis	10.21037/apm-21-2669	Cancer
7	Kaempferol, Myricetin and Fisetin in Prostate and Bladder Cancer: A Systematic Review of the Literature	10.3390/nu13113750	Cancer
8	Does Probiotic Lactobacillus Have an Adjunctive Effect in the Nonsurgical Treatment of Peri-Implant Diseases? A Systematic Review and Meta-analysis	10.1016/j.jebdp.2020.101398	Dental
9	The Clinical, Microbiological, and Immunological Effects of Probiotic Supplementation on Prevention and Treatment of Periodontal Diseases: A Systematic Review and Meta-Analysis	10.3390/nu14051036	Dental
10	Diet, Obesity, and Depression: A Systematic Review	10.3390/jpm11030176	Depression
11	A systematic review on the mechanisms of vitamin K effects on the complications of diabetes and pre-diabetes	10.1002/biof.1569	Diabetes
12	The effect of microbiome-modulating probiotics, prebiotics and synbiotics on glucose homeostasis in type 2 diabetes: A systematic review, meta-analysis, and meta-regression of clinical trials	10.1016/j.phrs.2022.106520	Diabetes
13	Prebiotic and probiotic treatment of nonalcoholic fatty liver disease: a systematic review and meta-analysis	10.1093/nutrit/nuy031	Fatty Liver
14	Long-term nutrition support in gastrointestinal disease--a systematic review of the evidence	10.1016/j.nut.2011.07.004	GI
15	Berberine for the treatment of hypertension: A systematic review	10.1016/j.ctcp.2020.101287	Hypertension
16	British Dietetic Association systematic review of systematic reviews and evidence-based practice guidelines for the use of probiotics in the management of irritable bowel syndrome in adults (2016 update)	10.1111/jhn.12386	IBD
17	Review of the safety and efficacy of vitamin A supplementation in the treatment of children with severe acute malnutrition.	10.1186/1475-2891-12-125	Malnutrition
18	Migraine and Diet	10.3390/nu12061658	Migraine
19	Vitamin D receptor gene polymorphism and vitamin D supplementation on clinical/ treatment outcome in tuberculosis: current and future perspectives.	10.1080/14787210.2022.2081546	TB
20	Evidence-Based Role of Nutrients and Antioxidants for Chronic Pain Management in Musculoskeletal Frailty and Sarcopenia in Aging.	10.3390/geriatrics5010016	Non-Disease: Aging
21	Exercise alone or combined with dietary supplements for sarcopenic obesity in community-dwelling older people: A systematic review of randomized controlled trials	10.1016/j.maturitas.2018.02.005	Non-Disease: Aging
22	Impact of nutraceuticals and dietary supplements on mitochondria modifications in healthy aging: a systematic review of randomized controlled trials	10.1007/s40520-022-02203-y	Non-Disease: Aging
23	Micronutrient-gene interactions related to inflammatory/immune response and antioxidant activity in ageing and inflammation. A systematic review	10.1016/j.mad.2013.12.007	Non-Disease: Aging
24	Vitamin D supplementation in older adults: searching for specific guidelines in nursing homes.	10.1007/s12603-013-0007-x	Non-Disease: Aging
25	Evaluation of Dietary Patterns and All-Cause Mortality: A Systematic Review	10.1001/jamanetworkopen.2021.22277	Non-Disease: Diet and Mortality
26	Evidence-based evaluation of potential benefits and safety of beta-alanine supplementation for military personnel.	10.1111/nure.12087	Non-Disease: Military Diet
27	Rediscovering Tocophersolan: A Renaissance for Nano-Based Drug Delivery and Nanotheranostic Applications.	10.2174/1389450121666200611140425	Non-Disease: Nanotech
28	Can a probiotic supplement in pregnancy result in transfer to the neonatal gut: A systematic review	10.1111/aogs.13899	Non-Disease: Pregnancy
29	Serum 25-hydroxyvitamin D response to vitamin D supplementation in infants: a systematic review and meta-analysis of clinical intervention trials	10.1007/s00394-019-01912-x	Non-Disease: Infant
30	Vitamin D from Supplements Consumed during Infancy and Toddlerhood and Bone Health: A Systematic Review	10.52570/NESR.DGAC2020.SR0304	Non-Disease: Infant

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31	Vitamin D from Supplements Consumed during Infancy and Toddlerhood and Growth, Size and Body Composition: A Systematic Review	10.52570/NESR.DGAC2020.SR0303	Non-Disease: Infant
32	The effect of additional protein on lean body mass preservation in post-bariatric surgery patients: a systematic review	10.1186/s12937-021-00688-3	Non-Disease: Surgical treatment

The SRs can be broadly categorized as those dealing with disease and non-disease. 19 papers covered a variety of diseases/disorders: Autism, Diabetes, Hypertension, Irritable Bowel Disease, Alzheimer's, Depression, Cancer, Gastrointestinal Disorders, Migraine, Arthritis, Fatty Liver Disease, Malnutrition, Dental issues, and Tuberculosis. Of these four publications were on cancer, two on diabetes, two on dental issues, while the rest had one publication each. The remaining 13 papers we considered as non-disease. However, several of the non-disease papers involved conditions related to aging that may be considered as disorders (e.g., inflammation[9] and musculoskeletal frailty[10]). Of these 13, five were on aging, three on infancy, and the rest were singletons: dietary effects on pregnancy, military use, post-operative recovery, diet in general, and a synthetic nutraceutical compound – tocophersolan were covered (Table 1). Below we discuss the largest groupings - those SRs on nutraceuticals as they pertain to aging (five) and cancer (four), along with four that report on nutraceutical impact on childhood (three in general and one on autism).

Aging

The five papers on geriatrics and nutraceuticals [9–13]are disparate in their scope and evaluations, making it difficult to draw any meaningful conclusions. Four are SRs[9,10,12,14], and one a narrative review [13]. Martinez-Amat et al., in 2018 published an SR of RCTs that investigated effects of exercise interventions with or without nutritional supplementation for older adults with sarcopenic obesity. After an extensive literature search of over 2000 English language publications, they analysed eight published RCTs. The authors note some positive impacts of exercise, however determine that the diversity of the eight RCTs precludes meaningful conclusions[11]. Perna et al., in 2020 published a thorough SR of RCTs, cross sectional, and, observational studies, that investigated the role of nutraceuticals in geriatric pain management. Of 200 articles that met their initial search, they selected 49 for review. They conclude that the papers show significant beneficial roles for specific nutrients (proteins, amino acids, omega-3-fatty acids, magnesium, and vitamin D, as well the botanicals curcumin, and ginger), in long-term pain management especially for individuals with age-related sarcopenia and frailty[10]. Lippi et al., in their recent publication (August 2022), presented an SR of RCTs investigating the effect of dietary supplements on mitochondrial activity in the elderly. Of the initial 8489 records they screened, rather disappointingly, only six were included in the final review. However, the six papers together assessed over 200 individuals and the authors conclude that the RCTs in general support positive impacts from various dietary supplements (sodium nitrite, N-3-polyunsatuarted fatty acids, nicotinamide riboside, hydrogen-rich water, urolithin A, and whey protein) on mitochondrial function and morphology[12]. Unfortunately, we were unable to access the full-text of the Mocchegiani et al., manuscript[9] whose SR focussed on micronutrient-gene interactions in ageing and inflammation. Finally, the narrative review

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by Rolland et al., present conclusions from discussions of the French Group of Geriatrics and Nutrition, that strongly advocate for supplementation of vitamin D for nursing home residents sans prior deficiency evaluations. Though not an SR, this paper amplifies the experience of geriatric care specialists that vitamin D as a nutraceutical is well-tolerated and widely beneficial for the elderly[13]. In summary, the five papers together support a trend of positive impacts for nutraceutical use by the elderly, however they unanimously heavily emphasise the need for more studies, especially to rule out negative impacts, as well as determine better prescription doses and modalities.

Cancer

In contrast to the previous, the four SRs on cancer are highly specific in their focus. Crocetto et al., investigate the impact of three types of flavonols – kaempferol, fisetin and myricetin- all found in a variety of common foods on prostrate and bladder cancer, specifically whether they exert anti-neoplastic activity. It is telling that even with such a narrow focus the authors were able to extract a total of 49 unique studies. They published their results in 2021, concluding there was consistent evidence of anti-cancer impacts for all three nutraceuticals reported, and therefore strongly advocate for serious clinical studies probing the use of these nutraceuticals in prostrate and bladder cancer[15]. Another study published in the same year, analyzed 11 RCTs on nutraceutical effects on immune system function for post-operative liver carcinoma[16]. This SR has the advantage of assessing publications in both the Chinese and English languages. They present a rigorous analysis of 11 RCTs they filtered out from over 1800 publications screened. The included studies cumulatively include over 700 patients. They conclude that many immune biomarkers showed significant change upon treatment with a variety of probiotics and microecological agents, in patients with hepatocellular carcinoma as part of their postoperative management[16]. A paper published this year (2022) attempted a more ambitious screen. Johal et al., reviewed reports on the impact of nutritional interventions for patients with metastatic cancer experiencing cancer-associated malnutrition, sarcopenia and frailty[17]. Of over 8000 initial records they selected, 48 papers (18 RCTs among them) met their inclusion criteria for this scoping review. The nutraceuticals covered were broad; vitamins, minerals, antioxidants, proteins, amino acids, and fatty acids among them. The authors concluded that overall a consistent positive impact for multimodal treatments, and for omega-3-fatty acid supplementation was observed, but it was difficult to obtain as clear a picture for the other nutraceuticals primarily due to insufficient data[17]. The fourth paper in this series was published much earlier - in 2013 - and is an SR of reports on nutritional intervention roles for head and neck squamous cell cancer patients' who are undergoing radiotherapy or chemotherapy[18]. From an initial screen of 1141 publications, they included 12 in their final analysis, and report that no consistent pattern was observed, however point out that four of the 12 papers demonstrate significant positive benefits due to the nutraceutical intervention compared to controls[18].

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Childhood conditions

A highly anticipated comprehensive SR of pharmacological and dietary supplementation in the treatment of pediatric autism, unfortunately yielded results too varied which the authors state precludes them from deriving meaningful conclusions[19]. The SR, published in 2017, was a true attempt to derive profiles useful for personalized treatment for autism. Upon an extensive literature search, they identified several dozen RCTs that cumulatively included almost 2000 participants, where specific treatment and specific disease profiling was reported. However, despite the large sample size the authors conclude the lack of consistent phenotyping greatly hampered an accurate assessment, as the number of variables used in characterization was too great[19].

The other three SRs dealing with children do not specifically address any disorder. One is a recent SR of vitamin D supplementation in infants[20]. Zitterman et al., included 61 studies in their final analysis totalling over 1800 participants. Encouragingly, from their SR, they were able to definitively conclude that a daily dosage of 400 IU of vitamin D was sufficient to prevent nutritional rickets in children, was well below the toxicity threshold, and thus this nutraceutical could be administered universally sans need for personalized or precision approaches[20]. However, these conclusions are challenged by another SR published in the same year, by the USA Dept. of Agriculture (USDA), Food and Nutrition Service as part of the 2020 Dietary Guidelines Advisory Committee publications on Nutrition Evidence SRs (NESR). The USDA NESR reported that there was insufficient evidence to conclude any effect on bone health (including markers for rickets) for children under the age of two years old due to daily supplementation of 400 IU of vitamin D versus a lower dose [21]. However, they only included 6 RCTs in their analysis and only one of those six papers investigated vitamin D dosage of 400 IUs versus a lower dose. The rest compared 400 IU/daily versus higher doses. Thus, this paper[21] cannot robustly challenge the previous SR from Zitterman et al.[20]. Finally, the last SR in this category is also a publication from the same USDA NESR; here iron supplementation for children under 2 years old and relationship to growth, size and body composition was reviewed[22]. This publication is important because it determines that there is moderate evidence for the possible slower growth of milk-fed infants who are supplemented with iron, versus those who are not supplemented. It also states there is insufficient evidence to determine what effect iron supplementation in infancy has upon growth and body composition[22]. Again, the number of papers included in the analysis is small, totalling only 10 studies. However, the potential adverse impact on growth due to iron supplementation in infants draws special attention.

Overview of all articles

Scope

The publications in our *file A* totalling 598 unique articles, cover a vast array of disorders, diseases, conditions, as well as a plethora of nutraceuticals, assessed via many scientific methods, and in many organisms, in addition to human studies. In order to obtain a landscape view of the scope of all of them, we began with refining all articles by their reported keywords. We

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used both Rayyan's keyword extraction feature as well as manually extracted keywords from all PubMed records and compared yields. Rayyan returned 468 unique keywords, and the PubMed manual extraction returned 1988 unique keywords, across all 598 articles. Assessment of the PubMed keywords however were not blind to capitalization, syntax, and spelling discrepancies, as they are researcher-input native entries, and hence the true number of unique keywords is expected to be much less. Conversely the Rayyan extraction was not native and therefore yielded data requiring less manual cleaning, which was amenable to cursory landscaping as given next.

Rayyan returned a total of 1492 keywords (468 unique) from 486 of the 598 articles. 486 articles had one or more keywords, 78 had five or more keywords, while 40 papers reported 10 or more keywords (full breakdown is given in supplementary notes) encouraging further sorting. Of the 468 unique keywords 302 occurred as singletons (Supplementary Table 1). Only 14 unique keywords are found 20 or more times (Table 2), with the top three being Dietary_supplements (60 times), Probiotics (57 times), and Vitamins (51 times). This keyword scoping analysis corroborates the notion suggested by our manual cursory reading of the 598 articles, which is that while they provide a wide overview of nutraceutical use in various spheres, other than the broad categories of probiotics and vitamins, no specific nutraceutical has been highlighted. Nevertheless, we do note that these data indicate that probiotics and vitamins are commanding due attention as important players in the arena of nutraceuticals in personalized medicine.

Table 2: Unique keyword counts across the 598 articles we reviewed. Only keywords found over 20 times are given.

Number	Keyword	Number of occurrences
1	Dietary_Supplements	60
2	Probiotics	57
3	Vitamins	51
4	Vitamin_B_Complex	49
5	Vitamin_E	49
6	Folic_Acid	41
7	Riboflavin	41
8	Vitamin_D	40
9	Biotin	39
10	Vitamin_A	39
11	Vitamin_U	39
12	Arachidonic_Acid	35
13	Ascorbic_Acid	29
14	Tocopherols	24

Drug Interactions, Genomics and TM based personalization

We next screened the 598 articles, for papers that reported on drug interactions, genomic profiling, and TMS based personalization. Of the possible negative impacts of nutraceutical consumption, drug interactions are perhaps the most dangerous, and therefore we performed targeted searches for drug interactions. Disappointingly, Rayyan returned no results, while 19 and

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26 papers were returned by searching in Covidence and Excel (PubMed) respectively. Five papers returned by Covidence were not found in the PubMed results, of which one paper we excluded due to irrelevancy. Therefore 30 unique papers are found. Of these, 18 are review articles covering a wide range of disease and non-disease states, e.g., cancer[23–25], cardiovascular disease (CVD)[26], autism[19], type 2 diabetes[27]. Notably, five review papers focussed on the microbiome[25,28–31]. While it is not possible to synthesize the findings of all 30 papers, we collate them in Table 3, and offer remarks on a select few that highlight a true personalized medicine or precision medicine approach to nutraceutical use.

Table 3: Articles that report drug interactions for nutraceuticals in personalized medicine

	Title	DOI	PMID	Comment
1	The oral microbiome in health and disease and the potential impact on personalized dental medicine	10.1111/j.1601-0825.2011.01851.x	21902769	Review
2	Irritable bowel syndrome: the evolution of multidimensional looking and multidisciplinary treatments	10.3748/wjg.v20.i10.2499	24627587	Review
3	Determining the optimal dose in the development of anticancer agents	10.1038/nrclinonc.2014.40	24663127	Review
4	Ayurnutrigenomics: Ayurveda-inspired personalized nutrition from inception to evidence	10.1016/j.jtcme.2014.12.009	26587393	Review
5	Contemporary views on the genetics of anorexia nervosa	10.1016/j.euroneuro.2016.02.008	26944296	Review
6	The metabolic role of the gut microbiota in health and rheumatic disease: mechanisms and interventions	10.1038/nrrheum.2016.68	27256713	Review
7	A comprehensive systematic review and meta-analysis of pharmacological and dietary supplement interventions in paediatric autism: moderators of treatment response and recommendations for future research	10.1017/S0033291716003457	28091344	Review
8	The protean role of haptoglobin and haptoglobin genotypes on vascular complications in diabetes mellitus	10.1177/2047487318776829	29799294	Review
9	Nutraceutical-based Integrative Medicine: Adopting a Mediterranean Diet Pyramid for Attaining Healthy Ageing in Veterans with Disabilities	10.2174/1381612824666181003113444	30280661	Review
10	Food Bioactive Compounds and Their Interference in Drug Pharmacokinetic/Pharmacodynamic Profiles	10.3390/pharmaceutics10040277	30558213	Review
11	Gut microbiota contributes towards immunomodulation against cancer: New frontiers in precision cancer therapeutics	10.1016/j.semcancer.2020.06.006	32580023	Review
12	Network Medicine Approach in Prevention and Personalized Treatment of Dyslipidemias	10.1002/lipd.12290	33118184	Review
13	Breakthroughs and Bottlenecks in Microbiome Research	10.1016/j.molmed.2021.01.003	33563544	Review
14	Multiple Molecular Mechanisms to Overcome Multidrug Resistance in Cancer by Natural Secondary Metabolites	10.3389/fphar.2021.658513	34093189	Review
15	Nanoparticulate Drug Delivery Strategies to Address Intestinal Cytochrome P450 CYP3A4 Metabolism towards Personalized Medicine	10.3390/pharmaceutics13081261	34452222	Review

16	The Challenge and Importance of Integrating Drug-Nutrient-Genome Interactions in Personalized Cardiovascular Healthcare	10.3390/jpm12040513	35455629	Review
17	Role of gut microbiota in the immunopathology of atherosclerosis: Focus on immune cells	10.1111/sji.13174	35474231	Review
18	Vitamin D receptor gene polymorphism and vitamin D supplementation on clinical/ treatment outcome in tuberculosis: current and future perspectives	10.1080/14787210.2022.2081546	35608034	Review
19	Nutrigenetics and nutraceuticals: the next wave riding on personalized medicine.	10.1016/j.trsl.2006.09.003	17240315	
20	A translational bioinformatic approach in identifying and validating an interaction between Vitamin A and CYP19A1	10.1186/1471-2164-16-S7-S17	26100049	
21	Mining Biomedical Literature to Explore Interactions between Cancer Drugs and Dietary Supplements		26306241	
22	Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder	10.1038/tp.2016.29	26978738	
23	MAPK signalling pathway in cancers: Olive products as cancer preventive and therapeutic agents	10.1016/j.semcancer.2017.09.002	28912082	
24	Fundamental Considerations for Genetically-Guided Pain Management with Opioids Based on CYP2D6 and OPRM1 Polymorphisms.		30508992	
25	Personalized Nutrition: Translating the Science of NutriGenomics Into Practice: Proceedings From the 2018 American College of Nutrition Meeting	10.1080/07315724.2019.1582980	31099726	
26	Alzheimer's Disease and Parkinson's Disease: A Nutritional Toxicology Perspective of the Impact of Oxidative Stress, Mitochondrial Dysfunction, Nutrigenomics and Environmental Chemicals	10.1080/07315724.2019.1683379	31829802	
27	Variable Genomic and Metabolomic Responses to Varying Doses of Vitamin D Supplementation	10.21873/anticanres.13982	31892609	
28	The acute effect of metabolic cofactor supplementation: a potential therapeutic strategy against non-alcoholic fatty liver disease	10.15252/msb.209495	32337855	
29	GABA-producing Lactobacillus plantarum inhibits metastatic properties and induces apoptosis of 5-FU-resistant colorectal cancer cells via GABA(B) receptor signaling.	10.1007/s12275-021-0562-5	33527319	
30	Genome-wide association study of fish oil supplementation on lipid traits in 81,246 individuals reveals new gene-diet interaction loci	10.1371/journal.pgen.1009431	33760818	

The first is a review of the interaction between dietary products that contain CYP3A4 (a type of cytochrome P450) modulating compounds, and pharmaceutical drugs that target CYP3A4, focussing on reports of interactions when taken together either with or without health care professional's input[32]. In particular the authors highlight the adverse effects reported due

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to intake of grapefruit juice with felodipine in individuals with hypertension[33], and collate other reports of similar interactions, concluding that there is a need for more careful assessment of possible interactions prior to dosing, and also suggesting potentially protective drug delivery methods[32].

The second paper we remark on is a paper suggesting and explaining a field of study they term 'ayurnutrigenomics'. Here the focus is entirely on how nutraceutical usage is (historically and currently) deployed in Ayurveda, which is a true personalized medicine TMS[3]. The authors discuss the ayurvedic equivalent of a genetic constitution, 'prakriti' with respect to the three dosha constitutional-typing of the individual as part of the personalized approach in ayurvedic medicine. This paper is noteworthy as it correctly explains the TMS basis for nutraceutical dosing, and importantly, clarifies that dietary products in personalized TMS are considered medicines, and therefore should not be taken only as per individual preference.

We note a detailed review by Briguglio et al., published in 2018 that discuss how foods and beverages may interact with drugs via pharmacokinetic or pharmacodynamic modulation[34]. It provides detailed tables of nutraceutical compounds and their possible interactions with various pharmaceuticals. The authors note that the burgeoning use of complimentary and alternative medicine substances poses the potential for growing adverse drug reactions, especially in patients with renal, hepatic or gastro-intestinal conditions. However, they note that the majority of studies in food-drug interference are from animal or *in vitro* models with a paucity of robust human studies[34].

Finally, we draw attention to the review just published (2022) on drug-nutrient-genome-interactions and their impact on treatment for patients with CVD[26]. In particular, the authors discuss evidence for nutraceutical interaction with drugs commonly prescribed for CVD. As in other reviews[32,35,36], the majority of clear evidence to date centers on the cytochrome enzyme family members, however notably, here the authors tie that to genetic profiles (both tested and ethnicity-based expectations) of CYP enzyme metabolism. In another instance, they discuss the impact of genetically determined specific membrane transporter profiles on nutraceutical-drug interactions, emphasizing the possible impact of the individual's genomic background. They conclude that genetically guided nutritional advice would be necessary in order to mitigate potential adverse interactions, but can also be potent in enhancing beneficial nutraceutical-drug interactions in CVD treatment[26].

Nutraceuticals and COVID-19 (Sars-CoV-2)

As mentioned earlier the PubMed keyword extraction proved unwieldy, requiring extensive manual data cleaning. However, upon initial data refinement it was observed that the PubMed keyword extraction closely mirrored that from corroborating those findings from Rayyan, and therefore we will not repeat them (supplementary table 1). Curiously though, the PubMed keyword extraction yielded 11 times the keyword 'COVID', one entirely absent from the Rayyan extraction. We then manually searched PubMed for articles within our 598 that were related to Covid-19, and found 15 relevant papers (Table 4). Six of them are reviews [37–42], two studies provide perhaps the

clearest evidence on the subject[43,44]; one is a comparative study that perhaps provides the clearest evidence on the subject [44]. It is a retrospective report on 311 patients with severe Covid-19, treated in February of 2020 at the Wuhan Union Hospital, China. Li et al., report that 75.6% of 123 patients treated with probiotics survived to hospital discharge and remained virus-negative for significantly longer than patients not given probiotics[44]. The second is an observational case-control study of 66 Covid-19 survivors divided into two groups of equal number. One was given a nutritional supplement of amino acids, vitamins B1 and B6, malic, succinic, and citric acids while the other did not receive any. Biometric data was collected after eight weeks, and the authors concluded a clear positive quality of life and recovery improvements dur to the intervention[43]. Two reports from Italy, detail doctor's experience of prescribing nutraceuticals during in-patient care, one center administered whey proteins, and intravenous infusions of multivitamins and trace elements as well as targeted vitamins upon detection of deficiencies[45], while the other reports on 94 patients (49 in ICU) who were given high-protein and high-calorie personalized nutritional regimens[46]. One paper details general public's nutraceutical usage trends during the pandemic in Poland. Another study of note is a metabolomics profiling conducted on 51 healthcare workers that showed a higher monolaurin signature in the blood of healthcare workers who demonstrated better protection to infection[47]. Monolaurin is a metabolite of coconut fat, and the researcher link their findings to possible dietary modulations for healthcare professionals. The remaining publications are letters, or perspectives produced by authors from predominantly non-western locations, where it may be assumed nutraceuticals as part of TMS treatments for Covid-19, was more widespread than in the west. Together, they echo each other's calls for renewed global attention to nutraceuticals as agents promoting pandemic preparedness.

Table 4: 15 Articles on nutraceuticals in personalized medicine with relation to Covid-19 pandemic. *particularly important studies.

	Title	DOI	Comment
1	Dietary Recommendations for Post-COVID-19 Syndrome	10.3390/nu14061305	Review
2	N-Acetylcysteine as Adjuvant Therapy for COVID-19 -A Perspective on the Current State of the Evidence.	10.2147/JIR.S306849	Perspective (China)
3	Understanding protection from SARS-CoV-2 using metabolomics	10.1038/s41598-021-93260-2	Metabolome of health care workers study
4	The Strategy of Boosting the Immune System Under the COVID-19 Pandemic	10.3389/fvets.2020.570748	Review
5	Therapeutic supplementation with zinc in the management of COVID-19-related diarrhea and ageusia/dysgeusia: mechanisms and clues for a personalized dosage regimen.	10.1093/nutrit/nuab054	Letter/Perspective (Brazil)
6	Nutritional management of individuals with SARS-CoV-2 infection during rehabilitation	10.22540/JFSF-07-088	Review
7	The probiotic Bifidobacterium in the management of Coronavirus: A theoretical basis	10.1177/2058738420961304	Review

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8	Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol	10.1016/j.nut.2020.110835	In-patient treatment experience
9	The Role of Diet and Supplementation of Natural Products in COVID-19 Prevention	10.1007/s12011-021-02623-3	Communication (multi-country)
10	The Impact of the COVID-19 Pandemic on the Composition of Dietary Supplements and Functional Foods Notified in Poland.	10.3390/ijerph182211751	Nutraceutical usage trends in general population in Poland during pandemic
11	The role of probiotics in coronavirus disease-19 infection in Wuhan: A retrospective study of 311 severe patients.	10.1016/j.intimp.2021.107531	Comparative study (Wuhan)*
12	Nutritional therapy for patients with coronavirus disease 2019 (COVID-19): Practical protocol from a single center highly affected by an outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection	10.1016/j.nut.2020.111048	In-patient treatment experience
13	A Review on Measures to Rejuvenate Immune System: Natural Mode of Protection Against Coronavirus Infection	10.3389/fimmu.2022.837290	Review
14	Ways to Address Perinatal Mast Cell Activation and Focal Brain Inflammation, including Response to SARS-CoV-2, in Autism Spectrum Disorder	10.3390/jpm11090860	Review
15	Effects of a New Multicomponent Nutritional Supplement on Muscle Mass and Physical Performance in Adult and Old Patients Recovered from COVID-19: A Pilot Observational Case-Control Study.	10.3390/nu14112316	Observational case-control study (Italy)*

Summary

In summary, a scoping review of these articles indicate that data currently available is still preliminary, and while the community recognizes the potential for nutraceuticals to interact with drugs, there is yet a significant lack of robust studies that adequately investigate the matter, either for positive or negative interactions. Coupled to this the current literature exhibits an awareness that the field of nutraceutical usage is inherently rooted in TMS systems, which are based on a foundation of personalized medicine. Thus, a true understanding of drug interactions is presupposed to require advanced modern personalization methods such as, even precision-genomic-typing based methods. The papers we have highlighted here draw attention to these broad strokes of understanding, which are echoed by the literature we have scoped for this review. Finally we re-iterate the suggested notion that nutraceuticals confer immune protection, as evidenced by the number of papers published just during the Covid pandemic on the issue.

Limitations of this review

This review paper is by no means comprehensive nor is it a systematic review of the literature. It is intended to be a mini-scoping of the trends unearthed by current literature on nutraceuticals as they are being used in personalized or precision medicine. Thus, papers were only sourced from PubMed as the number and breadth of literature yielded from that repository

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alone was large, and deemed sufficient to derive a preliminary scoping of broad conclusions. Therefore, there are almost certainly, many more papers extant in other repositories on this topic that may have not been included. However, we limited our analysis to PubMed as it is the gold standard repository for scientific publication indexing and has provided a sufficient as well as trustable source for the purposes of this preliminary landscaping analysis.

A significant limit of this work is that the deliberate broadness of the question it set out to answer precludes ability for rigorous filtration of the papers reviewed. Therefore, while we have discussed trends from the SRs on the subject, as well as trends from other selected sub-sets of the literature, again it is possible we may have missed important conclusions. To ameliorate this possibility, we conducted a keyword scoping for all 598 papers in our initial search result, which provided some degree of scoping. However, we understand that keywords are entirely based on researcher volunteered submissions and hence not completely objective. However, by analyzing keywords by two different methods (Rayyan output and native PubMed keywords) and detecting similar result trends (supplementary table 1), lent confidence to the veracity of this approach.

CONCLUSION

The vast majority of studies on nutraceuticals as personalized or precision medicine, have only been published since the advent of the new millennium indicating the novelty of the field. The number of publications however, confirm that we are very much in an exponential growth phase of this focus of research, as we move through the third decade of the 21st century, and thus we expect the number, quality, breath and scope of publications to increase. Publications to date are highly diverse and disparate in their methods, condition focussed on, and analyses mores, significantly impeding efforts to obtain specific conclusions. Nevertheless, the vast majority of studies we surveyed, reported positive effects of nutraceuticals as agents to improve health or even as therapeutics (usually under the sphere of TMS as part of complimentary and alternative medicines[1]), either as already evidenced, or enthusiastically anticipated. They cover a huge swath of diseases, disorders, and conditions, from infancy to adulthood to old age and even impacts on mortality (Table 1). Somewhat lagging behind are publications focussed on possible or reported adverse effects due to nutraceutical use (Table 3). These raise the alarm as nutraceuticals are becoming more widely adopted by the general public usually without professional input. Another important observations is the fact that the Covid pandemic of the past two years has led to many centers (particularly in the non-western world) adopting nutraceuticals as part of their emergency response treatments, as well as investigating their impact on protection from disease (Table 4). We anticipate the number of publications in this sphere to grow as time increases and professionals are able to gather their experiences and data toward publication. The fact that 'COVID' was among the highest number of keywords returned from our scoping of PubMed keyword entries on nutraceuticals in personalized medicine is noteworthy. It indicates the present interest in exploring the full potential of nutraceuticals as a yet predominantly untapped resource.

Non-standardization of nutraceuticals greatly contributes to impeding efforts to accurately assess risks for adverse events, as well as to thoroughly

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investigate potential for positive impacts. Indeed, the one common theme among almost all papers we reviewed was the call for further studies, particularly robust reproducible scientific research. With respect to this, from our scoping of the field, we posit two vital questions that require concerted efforts to answer: Firstly, is it possible to treat nutraceuticals as true therapeutics, i.e., with standardized dosages and treatment methodologies implemented? And secondly, what is the connection between nutraceutical usage and underlying individual's genomics/genetic profiles and how do these interact. It is essential we fill these gaps in our understanding, so that we may fully benefit from nutraceuticals as a modern personalized and precision medicine substance.

Nutraceuticals are easily obtained, cheap, largely non-toxic, and have the potential for enormous benefit for health and wellbeing, not least of which was evidenced during the Covid pandemic. Their proven efficacy in TMS is poised to translate well into modern WMM as investigations grow into their use in personalized and precision medicine.

Supplementary Materials

Supplementary Note 1 – Details of PubMed MeSH search terms, and keyword counts

Supplementary Table 1 – Total counts for unique keywords returned from Rayyan and PubMed yields.

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